THE DEVELOPMENT OF THE CONDUCTING SYSTEM IN THE HEART OF SHEEP

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The views that have been put forward with regard to the development of the conducting system fall into two main categories as follows.

(1) Persistence of original atrioventricular (A-V) canal tissue (Mall, 1912; Koch, 1922).
(2) New formation.
  (*a*) *In situ*—A-V canal and ventricle (Wahlin, 1935; Sanabria, 1936).
  (*b*) From sinus musculature—with secondary migration distally (Retzer, 1908).
  (*c*) From A-V canal with secondary migration distally (Shaner, 1929; Walls, 1947).
  (*d*) From ventricle with secondary migration proximally (Stiénon, 1925; Ohmori, 1928).

Tandler (1913), though inclined to agree with Retzer (1908) that the bundle was essentially a new formation, maintained that it was derived from the original A-V canal musculature. He pointed out, however, that on account of its special structure and development it should be regarded as a specific entity.

Wahlin (1935) has emphasized that the various suggestions as to the origin of the conducting system are not necessarily mutually exclusive. He himself looks upon the A-V node as " . . . ein Rest des Canalis auricularis . . . aber auch, wie die übrigen Abschnitte des atrioventrikulären Reizleitungssystems, als eine Neuerwerb wegen seiner ganz speziellen Differenzierung."

All the above authors regard the conducting system as being formed in continuity. Recently, however, Calcagno (1941*a*, *b*) has claimed that the A-V node and bundle develop independently in the bovine embryo and only become joined secondarily.

Side by side with these ontogenetic investigations certain workers have sought to establish the origin and significance of the system on phylogenetic grounds. Thus, Benninghoff (1923) looks upon it as the remnant of an originally extensive system of " Konturfasern " around which a condensed myocardium has been laid down. Davies (1942) adopting a more teleological standpoint, sees the system not as a remnant, but as a neomorphic development specially evolved in birds and mammals to meet the need for rapid dissemination of the cardiac impulse. In support of this view he adduces the claim made by several workers that the A-V bundle comes into existence before muscular continuity between atria and ventricles has been dissolved. In recent years, however, the whole conception of the conducting system, both as regards structure and function, has been strongly challenged by Glomset and his co-workers (1940–48) in a series of critical and provocative papers. In view of Glomset's criticisms and because preliminary investigation of the adult system showed that at least one important feature—the nervous component of the bundle—had received inadequate attention, the present investigation was undertaken to determine what help an ontogenetic study might afford in evaluating the significance of the system.

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Material and Methods

The animal studied throughout has been the sheep. The 18–20 day specimens reported on are in the collection of Professors W. J. Hamilton and J. D. Boyd, to whom the author is indebted for their loan. Several of the larger " timed " hearts were obtained through the kindness of the late Sir Joseph Barcroft, but the majority of specimens was collected over the course of the last three seasons at various abattoirs. Smaller embryos were sectioned *in toto* at 5–8μ, while from the larger ones selected blocks of tissue were examined. The plane of section was usually coronal, but where duplicate material was available sagittal sections were sometimes made. Staining was carried out by Heidenhain's iron hæmatoxylin, most often without counterstain. The crucial step of differentiation was always carried out by the writer himself and it was found that in this way more instructive and consistent preparations were obtained than by the use of the bulk impregnation method of Blair and Davies (1935). At intervals in a series, slides were stained by Best's carmine method for glycogen and by Bauer's method (using, however, sodium para-periodate as oxidizing agent instead of chromic acid). Some of the older specimens were stained by van Gieson and by Masson stains.

The material comprised (*a*) complete serial sections through 30 embryos between the *4-mm. and 22·5-mm. stages*, including embryos aged 18, 19, 20 (two specimens), 23, and 26 days; (*b*) complete serial sections through the hearts of 21 embryos between the *24- and 100-mm. stages*, and (*c*) runs of serial sections from blocks of tissue from 21 specimens between *115 mm.* and birth (580 mm.), including fœtuses aged 69 and 110 days (two specimens).

Observations

4–4·5-mm. stage. The cells in the posterior wall of the A-V canal in these specimens are orientated transversely so as to encircle the canal (Fig. 1). They are more open in appearance, though this may result from their direction rather than from true structural difference. This circular arrangement of cells at the A-V ostium is reminiscent of the similar arrangement described in this region in adult lower vertebrate hearts (v. Skramlik, 1921; Benninghoff, 1923). Sanabria (1936) described fine vacuoles within the cytoplasm of the cells of the posterior wall of the A-V canal, and their nuclei as more deeply staining, but such distinctions are not at all marked in the present material; for at this stage all the cells of the heart wall are vesicular in character, and if one were not looking deliberately for the first signs of specialization, there would be little to draw one's attention to the posterior wall of the A-V canal other than the orientation of the cells.

7·5–11-mm. stage. The earliest specialization of the myocardium is visible in these specimens. Along the inferior aspect of the dorsal endocardial cushion the cells are clearer and rather more vesicular than in the remaining myocardium (Fig. 2). The nuclei are deeply stained and often crenated. In the *8-mm.* bovine embryo, Wahlin (1935) also noted this shrunken and pyknotic appearance of many nuclei of the primitive bundle. Traced posteriorly the cells of the " bundle " become continuous with those of the posterior wall of the A-V canal behind the posterior endocardial cushion. This is a region in which active cellular proliferation has been described by some authors. Thus, Shaner (1929) found, in the calf, that the " A-V conduction apparatus begins with the laying down of the A-V node." This node he described as making its appearance at the *9-mm. stage* and becoming unmistakable as a projecting blob of frothy protoplasm by the *13–15-mm. stage*. He implied, though he did not explicitly state, that it was a migration of cells from this node which gave rise to the A-V bundle (p. 86). Walls (1947)—on the basis of two transversely sectioned hearts—follows Shaner's description and records an active growth process taking place from the node. Neither of these authors, however, offers convincing evidence—e.g. mitotic or amitotic figures—for such activity. The same criticism may be levelled at Retzer (1908) and Ohmori (1928), both of whom regard the bundle as reaching its definitive location by an active growth process. Sanabria (1936) speaks of " une prolifération—peut être aussi . . . une migration " as taking place behind the posterior endocardial cushion. Stiénon (1925) maintains that the bundle is formed by an upward

migration of cells from the spongy musculature that crowns the interventricular septum. But here again satisfactory evidence for an active migration is not apparent.

The sagittal section (Fig. 2) shows that it is along the under surface of the posterior endocardial cushion and not in the posterior wall of the A-V canal that earliest differentiation is found. The cells in the former situation were somewhat richer in glycogen than is the general myocardium. *There is no evidence whatsoever that the bundle arises by active growth from a distant focus either in the A-V canal or in the ventricle.* Rather the appearances seen in sagittal section taken together with the coronal picture suggest a local retention of more primitive features in a region where there is relative immobility—a suggestion first put forward by Keith and Flack (1906). The manner in

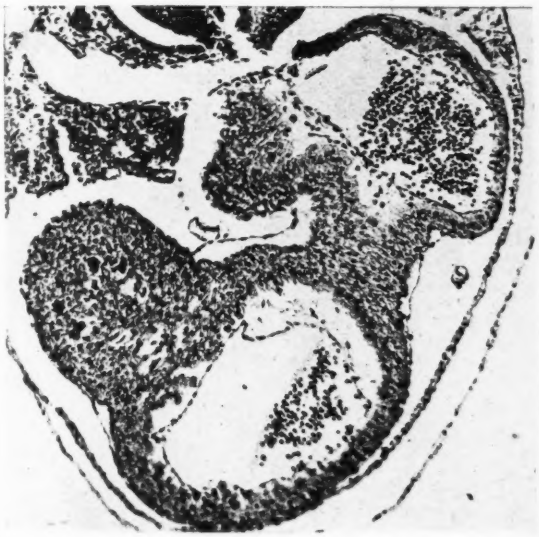

FIG. 1.—Coronal section through heart of 4-mm. (18 day) sheep embryo (B27). The section passes through the posterior wall of the A-V canal where the cells are seen to be arranged circularly. They are a little more "open" in appearance than in the rest of the myocardium. Magnification, ×90.

FIG. 2.—Longitudinal section through heart of 7·5-mm. embryo in the line of A-V the canal. The cells along the under surface of the dorsal endocardial cushion stain less deeply than the general myocardium. Note the close relation of this primitive bundle to the under surface of the cushion. Magnification, ×50.

which differentiation makes its appearance along the upper margin of the septum inferius suggests that relative fixity is an important conditioning factor. Thus, the characteristic open appearance of the cells is marked precisely where the upper margin of the septum abuts against the inferior aspect of the endocardial cushion (Fig. 3 and 4). Further forwards, opposite the interventricular foramen, such difference is much less marked. Progressive fusion of the septum inferius with the endocardial cushion leads to forward extension of the bundle. It may be, too, that relative richness in glycogen is associated with lesser activity. As the bundle anlage is traced posteriorly it passes behind the dorsal endocardial cushion intervening between it and the circularly disposed fibres of the A-V ostium. No signs of an A-V node are yet discernible.

At the *7·8-mm. stage* there is a tendency for the spongy trabeculæ which have made their appearance in the ventricles, to condense in part as two large bundles applied to the sides of the upper

part of the interventricular septum (Fig. 5), and it is within these trabeculæ that the branches of the bundle differentiate. A similar arrangement of the ventricular trabecular tissue has been noted by Wahlin (1935) and Sanabria (1936) for the bovine and sheep respectively, whilst Walls' (1947) illustration (pl. 4, fig. II) would seem to indicate a similar state of affairs in the human, too. Sanabria found that differentiation did not occur within these trabeculæ until their upper ends were firmly fused with the interventricular septum, and from this he argued that there was " . . . une induction . . . émanant des éléments du tronc commun. . . ." However, the effect of fixation against the interventricular septum may be the operative factor. At about the *11-mm. stage* (about 24–26 days) the interventricular foramen is closed, anchoring securely the upper part of the septum.

12–22-mm. stage. Once closure of the interventricular foramen has taken place and fixation at the upper end of the septum so increased, differentiation of the branches of the bundle proceeds

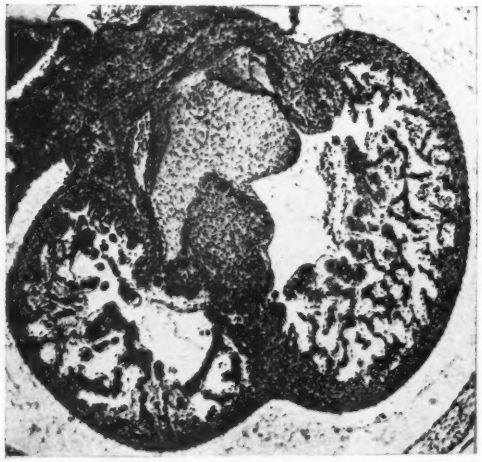

FIG. 3.—Coronal section through 9·2-mm. heart. The crus commune primordium is seen in the upper part of the interventricular septum abutting on the under surface of the septum intermedium. Note the trabecular meshwork which fills the ventricular cavities in large part. Magnification, × 50.

FIG. 4.—High-power view of crus commune shown in Fig. 3. The cells are more vesicular than are those of the general myocardium. Magnification, × 170.

rapidly. Whilst it is difficult to be sure of the exact stage at which interruption of muscular A-V continuity takes place, there seems no doubt that the bundle anlage is defined while such continuity yet exists. The interventricular septum is made up, especially in its upper part, of loosely compressed muscular trabeculæ, each of which is clothed by endocardium. Surmounting the septum the primitive bundle with its branches is draped in the form of an inverted U. Differentiation is more marked in the bundle itself than in its branches, and the bundle, too, is somewhat richer in glycogen than is the general myocardium. Peripherally there is not yet any Purkinje tissue to be made out. The whole bundle is voluminous and ill-defined. The A-V node is inconspicuous and, were it not specially sought, would hardly attract attention. It is the general direction of the cells of the bundle and its branches that catches the eye under the low power of the microscope. When examined under high magnification the differences between specialized and general myocardium are less prominent.

By the *14-mm. stage* atrioventricular continuity is largely interrupted. A small accumulation of cells in the inferior part of the interatrial septum is recognizable as the primordium of the A-V

node. Interposition of undifferentiated connective tissue between atria and ventricles is particularly well seen at the top of the interventricular septum where it is associated with the fibrous basis of the septal parts of the mitral and tricuspid valves. The connective tissue core of the mitral septal cusp extends well into the interventricular septum so that the bundle is displaced to the right and appears to circumvent the right side of the septal A-V connective tissue partition. The bundle so displaced may be reduced to a very thin structure, difficult to follow in serial sections. Continuity between the mass of cells in the foot of the interatrial septum construed as A-V node, and the bundle itself does not, however, seem to be broken.

The inverted U disposition of the branches of the bundle draped over the upper margin of the muscular interventricular septum becomes more obvious as development proceeds (Fig. 6), for the limbs of the U become drawn out as ventricular expansion goes on. Over the left face of the septum cells, which do not, however, differ much from those of the rest of the myocardium, are orientated in the line of the left branch of the bundle, whilst on the right side the branch appears to pass into a

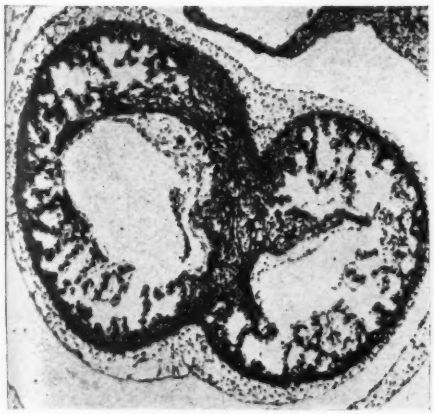

FIG. 5.—Transverse section through 7·8-mm. heart. Some of the ventricular trabeculæ are becoming consolidated against the interventricular septum. Magnification, × 50.

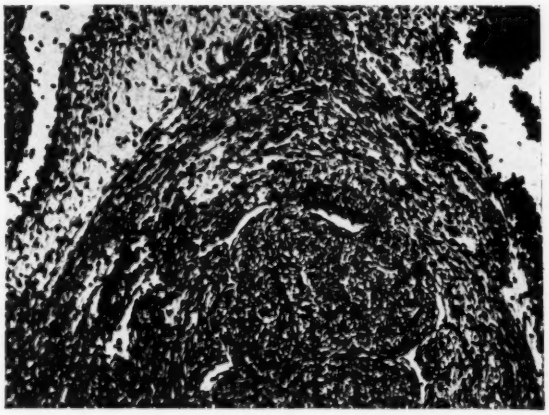

FIG. 6.—Coronal section of the upper part of the interventricular septum in an 18·8-mm. heart. Note the primitive bundle branches straddling the septum and passing away on either side of it. The specialized cells are somewhat vesicular. Magnification, × 100.

trabecular mass which is directed through the ventricular cavity towards the apex—the forerunner of the moderator band. The cells of the bundle and its branches are richer in glycogen than are those of the general myocardium (Fig. 13 and 14).

At the *18·5-mm. stage* there appear beneath the endocardium of both ventricles islands of clear and somewhat rounded cells with large rather pale staining vesicular nuclei (Fig. 7). These cells are not particularly rich in glycogen at first, and bear little resemblance to Purkinje cells. Gradually they become more numerous until they extend over the distal two-thirds of the ventricular lining.

Three hearts showed a small excess of glycogen in the left ventricle as compared with the right (Fig. 13). Differences in glycogen content of the various heart chambers, met with at later stages, will be described below.

By the *22-mm. stage* the A-V node is easily recognizable in the lowest and posterior part of the interatrial septum as a collection of clear cells which have not become orientated in the direction of either right or left atrial fibres. It is still the amassment of cells in this situation, rather than actual structural difference, that catches the eye, though the nuclei are larger and more vesicular than in

the adjoining atrial walls. One gets the impression that this feature is the result of less dense packing of cells, the node being situated at a null point between fibres passing off into the right and left atria. The displacement of the bundle towards the right noted above becomes accentuated by tilting of the uppermost part of the interventricular septum so that the tricuspid valve comes to be at a somewhat lower level than the mitral (Fig. 8).

The thickness of the ventricular wall is largely made up of muscular trabeculæ. These are in process of consolidation to form a compact mass. The clear subendocardial cells noted above are widespread beneath the endocardium. Sheets of these cells clothing trabeculæ are becoming trapped within the thickness of the ventricular wall. In this way, as becomes apparent in later specimens, an intramural network connected with the subendocardium comes into being. Because of the non-uniform distribution of the subendocardial cells, not every crypt between trabeculæ is lined by these clear cells. The crypts extend deeply into the heart wall—almost out to the epicardium. At first many have a labyrinthine connection with the ventricular cavity and may contain blood cells. But

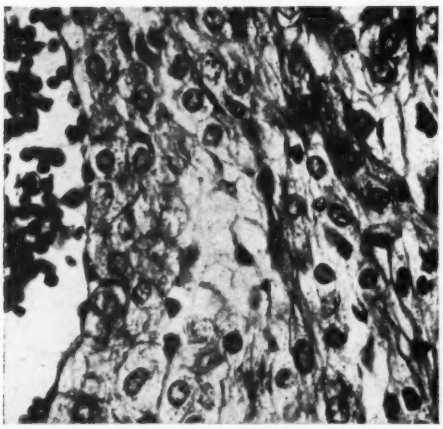

FIG. 7.—Longitudinal section of the left ventricle of 18·5-mm. embryo, showing clear subendocardial cells with pale vesicular nuclei. Magnification, ×200.

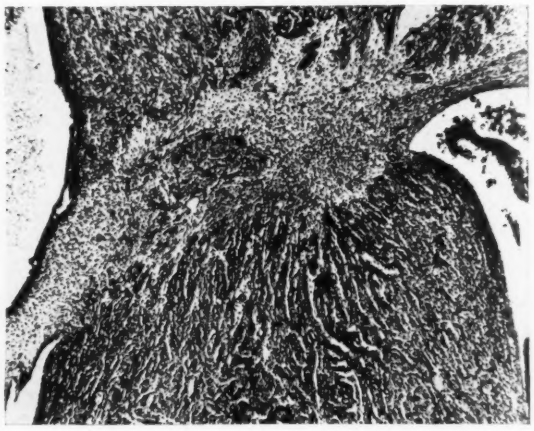

FIG. 8.—Coronal section through 100-mm. heart, showing displacement of the bundle towards the right. Magnification, ×80. Best carmine.

increase of the musculature leads to compression and obliteration of the great majority, whilst incomplete obliteration produces the appearance of small isolated " vessels " in the depths of the myocardium (cf. Fig. 18).

25–100-mm. stage. By the *25-mm. stage* the atrioventricular node, the bundle and the right and left branches have all been laid down, while indications of the peripheral elements of the conducting system have emerged. Various milestones in the further evolution of the system remain to be indicated.

Sagittal sections through the *28-mm. heart* shows the crus commune issuing from the node and passing forward along the top of the interventricular septum. The node is of loose texture, and neither in it nor in the rest of the system is muscle striation present though in the general myocardium it is well developed. Neuroblasts are not yet apparent in association with the node. The atria are richer in glycogen than are the ventricles but the conducting system shows no excess in this particular specimen.

In the *32-mm. specimen* nerve fibres were seen for the first time in the upper part of the A-V node, but neuroblasts could not be made out. The node and bundle were again not particularly rich in

glycogen; the left ventricle was, however, distinctly richer than the right. A well-defined moderator band was present in this specimen, which also showed clearly the displacement of the bundle to the right at the crest of the interventricular septum. The bundle branches became continuous with the large clear cells scattered beneath the endocardium. Here and there strands of these cells dipped into the mouths of intertrabecular clefts. Cell strands were to be found in the upper quarter of the ventricular wall, but they could not be followed into the thickness of the myocardium for any distance. These clear subendocardial cells were often no richer in glycogen than the rest of the myocardium and their vacuolated appearance cannot therefore be referred to glycogen accumulation as is the case in von Gierke's disease. An interesting incidental finding in this specimen was a marked difference in the glycogen content of the two atria (Fig. 15). The boundary between the chambers is remarkably sharp.

At *39 mm.*, groups of neuroblasts and nerves have made their appearance close to, but not quite within, the atrioventricular node. By *50 mm.* they are found actually within the substance of the node (Fig. 10).

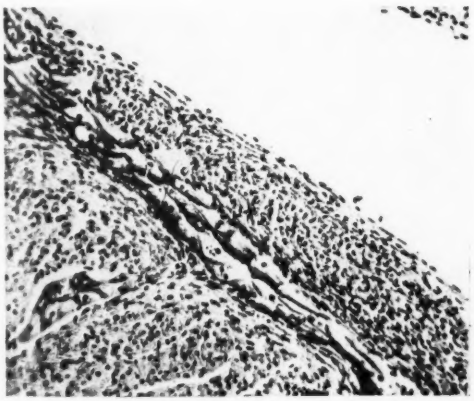

FIG. 9.—Strand of Purkinje cells laden with glycogen. Note the displacement of glycogen to the side of the cells. Interventricular septum of sheep at term. Magnification, ×130. Best carmine.

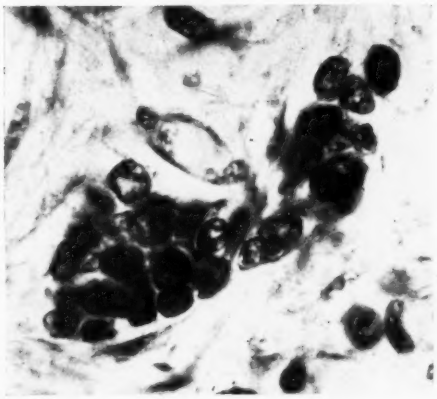

FIG. 10.—Neuroblasts within the atrioventricular node of a 50-mm. embryo. Magnification, ×1000.

The value of a glycogen stain for the identification of conducting tissue (Truex and Copenhaver, 1947) is well brought out in the *40-mm.* embryo. The somewhat flattened cells lining many of the intertrabecular clefts do not differ conspicuously from ordinary heart muscle cells. When stained for glycogen, however, they are readily differentiated by their high content (Fig. 11). Even at *70 mm.* the criterion of glycogen richness is the easiest means of picking out early Purkinje fibres, for there is little advance in histological differentiation (Fig. 12).

At *100 mm.* the cellular elements of the bundle branches are beginning to look much more Purkinje-like in character. The right branch in the upper part of the moderate band takes the form of more or less parallel strands of cells packed in connective tissue. Two features that characterize the mature Purkinje cell—perinuclear vacuolation and the occurrence of double nuclei—are beginning to make their appearance, though neither is yet marked. Striated fibrils are present in the marginal part of the cytoplasm, while around the nucleus staining is diffuse and reveals no special structure.

When the right branch is followed in serial sections it may be traced in the moderator band to the parietal wall of the right ventricle. Here it penetrates deeply into the muscle, giving off small

shoots which gradually fade out as they are traced serially. It is very difficult to say what is their fate but apparently they become continuous with ordinary muscle fibres, though actual transitions such as are common at later stages could not be made out. The A-V node is apparent as an agglomeration of fine anastomosing fibres containing many fibrils which are relatively poorly striated. A similar appearance is presented by the cells of the right and left atrium adjoining the fibrous A-V ring. The microscopic appearance of the A-V node cannot therefore be regarded as specific for that structure. It may be that proximity to a relatively fixed region (the fibrous ring) is the common factor responsible for these resemblances. Numerous ganglion cells and nerves are located all round the A-V ring and in the node itself especially in its posterior part.

FIG. 11.—Longitudinal section through left ventricle of a 50-mm. embryo. Along the line of the intertrabecular clefts strands of glycogen-rich cells have made their appearance. Histologically these cells are not very different from ordinary heart muscle cells. Bauer stain, without counterstain. Magnification, ×35.

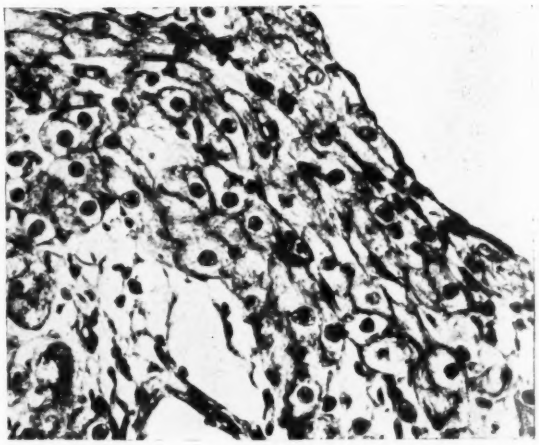

FIG. 12.—Moderator band in a 70-mm. heart. Purkinje cells have not yet made their appearance. Magnification, ×510.

The left branch of the bundle is well developed as a broad thin band under the endocardium of the left face of the interventricular septum. Some of the fibres of the left branch pass into small trabeculæ similar to the moderator band, but most continue down in the interventricular septum. Both branches are relatively richer in glycogen than the general myocardium.

Nerves are present over the surface of both ventricles—particularly richly on the left, as far down as the distal one-quarter.

145-mm. stage. Histological differentiation of Purkinje tissue within the ventricular walls has progressed so that strands of bloated cells are readily picked out under the low power. Many of the strands possess no insulating sheath of connective tissue, and in part of their course they may be orientated very differently from the surrounding myocardial fibres (Fig. 18). A perinuclear space is now more marked and binucleate cells common. The peripherally disposed fibrils pass from cell to cell and here and there striation is apparent. Cell boundaries are absent within the Purkinje

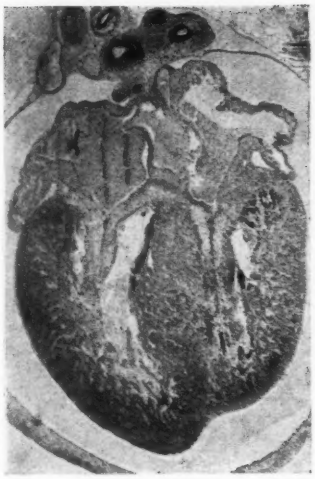

FIG. 13.—Heart of 18·8-mm. embryo, showing relative richness in glycogen of the left branch of the bundle passing down the left face of the interventricular septum. There is a slight excess of glycogen in the left ventricle as compared with the right. Best carmine. Magnification, ×18.

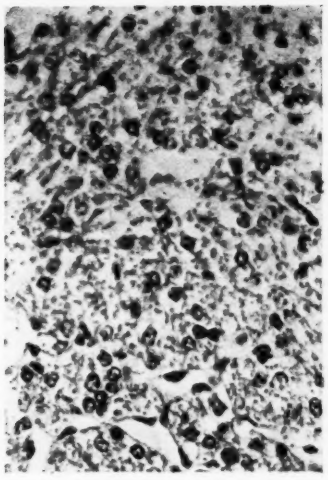

FIG. 14.—High-power view of the top of the interventricular septum (same specimen as Fig. 13) showing more glycogen in the bundle (above) than in the septum (below). Note the trabeculated constitution of the latter. Magnification, ×300. Best Carmine.

FIG. 15.—Transverse section through the upper part of the interatrial septum in a 32-mm. sheep embryo. In front are the roots of the aorta and pulmonary artery. The right atrium is considerably richer in glycogen than the left. The line of demarcation is remarkably abrupt under high magnification. Magnification, ×100. Best carmine.

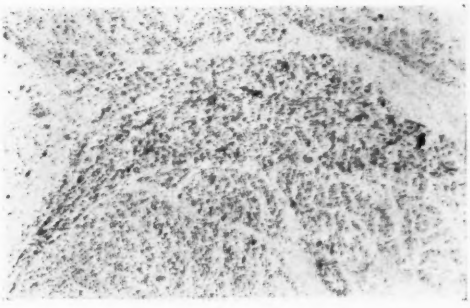

FIG. 16.—Bifurcation of A-V bundle in a 220-mm. embryo. There is considerable glycogen in the specialized tissue. Magnification, ×80. Best carmine.

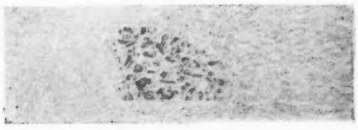

FIG. 17.—A-V bundle emerging from the fibrous A-V partition into the interventricular-septum (to the right of picture). There is rather less glycogen in the crus commune than in the bundle branches. Cf. Fig. 16. Magnification, ×80. Best carmine.

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strands as they are, too, in the ordinary myocardium. Mitotic figures are not to be found within Purkinje cells but appearances very suggestive of amitotic division are common. Not only nerve fibres but ganglion cells, too, are scattered over the ventricular walls (especially on the left side) as far as about half-way down whilst in the interatrial wall nerve cells and fibres are very abundant (Fig. 19). Many masses of cells, such as those illustrated, are scattered about in this region in every section.

250-mm. stage. The branches of the A-V bundle are embedded in a well-defined connective tissue bed, clearly brought out in sections stained by the Masson method, but the connective tissue sheath of the peripheral Purkinje strands does not stain well. The bundle branches (Fig. 16) and the peripheral strands of Purkinje tissue are rich in glycogen. The crus commune may be traced

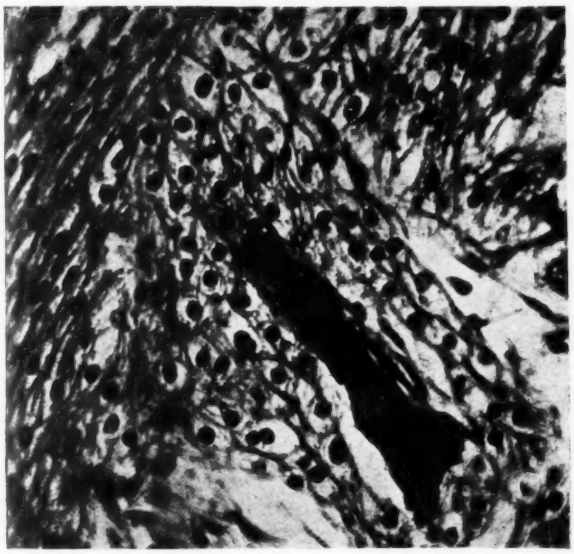

FIG. 18.—Strand of early Purkinje cells in left ventricle of a 145-mm. embryo. The blood vessel accompanying the strand is the remains of an incompletely obliterated intertrabecular crypt. Note the absence of a connective tissue sheath and the difference of direction as compared with the ordinary heart muscle. Magnification, ×410.

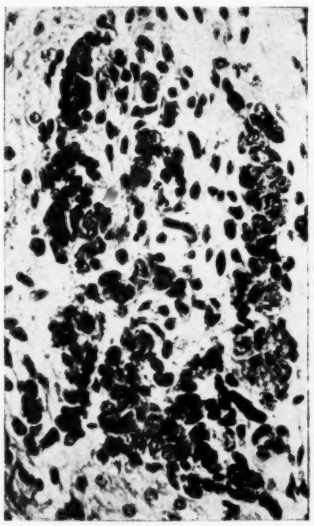

FIG. 19.—Masses of neuroblasts in the interatrial septum of 145-mm. heart. Magnification, ×295.

through the right part of the central cartilage of the heart. The glycogen content becomes less as the bundle is followed proximally and in the A-V node glycogen is no more abundant than in the ordinary atrial musculature (Fig. 17).

An interesting feature was observed in the interventricular septum of this specimen, namely the occurrence of stretch of Purkinje tissue intercalated in the course of an ordinary muscle fasciculus (Fig. 20). It will be referred to further below.

360-mm. stage. Strands of readily recognizable Purkinje tissue permeate the inner two-thirds of the ventricular walls. Many transitions to ordinary heart muscle cells can be seen. The great majority of the Purkinje cells are binucleated. An abundant Purkinje network is present beneath the endocardium, while in the epicardium numerous nerve bundles and occasionally collections of nerve cells are seen. These latter may be found over the upper two-thirds of the ventricles.

New-born stage. At the time of birth the Purkinje cells have reached their full development (Fig. 22). Strands of specialized cells stand out clearly when stained for glycogen (Fig. 9).

Sinu-atrial Node

Sanabria (1936) described in the *7-mm. embryo* a rudiment of the sinu-atrial node at the cavo-auricular junction. He described it as consisting of fine fibres staining poorly, and having nuclear chromatin arranged in the form of " un long filament pelotonné sur lui même." A careful search both in transversely and in longitudinally sectioned embryos at this stage has revealed only a mass of undifferentiated cells in the region mentioned by Sanabria without the characteristic nuclear

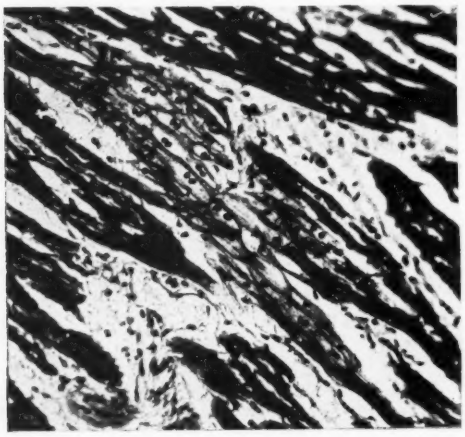

Fig. 20.—Purkinje fibres intercalated in the course of a stretch of ordinary heart muscle fibres. Left ventricle of 220-mm. embryo. Magnification, ×130.

Fig. 21.—Sinu-atrial node of a 360-mm. sheep. The musculature of the node is pale staining and primitive in appearance. It extends from the epicardium to the endocardium. Large nerve trunks and ganglionic masses such as those visible are common, especially on the epicardial aspect of the node. The characteristic artery of the node can be seen. Magnification, ×27.

appearances he describes. Because it is known that the sinu-atrial node will develop in this situation this mass of cells may be looked upon as its forerunner.

At the *22·5-mm. stage* there is still no histological specialization of the sinu-atrial node, though the mass of cells within the thick base of the right venous valve is conspicuous and may be taken to be its representative. The right venous valve in this specimen is prolonged to fuse with the lower and posterior part of the interatrial septum and such an arrangement may, perhaps, form the basis for the description given by Retzer (1908) of the origin of the conducting system from the sinus musculature.

Even at *40 mm.* little histological differentiation has occurred in this cell mass at the cavo-atrial junction. The cells have retained their clear, somewhat swollen and embryological appearance, whilst round about differentiation has progressed. The rudiment of the small artery that characterized the adult node may be seen here and there in serial sections at this stage. Masses of ganglion

cells are found on the epicardial aspect of the node. This apparent local lag in development shown by the cells of the node persists and becomes more noticeable so that by the *360-mm. stage* the node stands out clearly under the low power of the microscope as a pale staining mass of cells grouped round a small artery, and extending from endo- to epi-cardium (Fig. 21). Cross-striation is readily demonstrable with Heidenhain's hæmatoxylin. The same appearances are present in the new-born heart.

FIG. 22.—Purkinje fibres from the left ventricle of sheep at term. Note the striation in the peripheral part of the " cells " and the appearance of cell boundaries made by intersection of myofibrillæ. Magnification, × 880.

DISCUSSION

Sinu-atrial node. Structural specialization in the sinu-atrial (S-A) node is generally agreed to occur later than in the other conducting tissues of the heart. Sanabria (1936), however, reported thickening of the auricular myocardium in the sulcus terminalis as early as the *7-mm. stage*, and histological differentiation at *10 mm.* (sheep). In the present material no distinguishing features could be made out in the cells of the S-A node region until a relatively late stage (about *100 mm.*), though, armed with the knowledge that a node will develop in the sulcus terminalis, one may interpret the mass of cells at the base of the right venous valve as its primordium. But this mass of cells—whose raison d'être is apparently to be sought in the form of the valve root—while it may be singled out arbitrarily under the low power of the microscope and dignified with a name, loses all claim to distinction when examined at high magnification. The writer is aware of no high-power photograph demonstrating the early histological differentiation of the node claimed by several authors (Sanabria, 1936; Walls, 1947). What distinguishes the cells is rather the retention of primitive embryonic characters (e.g. poor striation and narrowness) whilst all around atrial cells go on maturing. This poor development is probably to be sought in the special location of these cells in a relatively quiet region, where they are not called upon to undertake energetic contraction. This suggestion finds support in the work of Glomset and Glomset (1940) who, in a review of

the structure and function of the S-A node in a number of mammals, showed that " the fibers . . . in the bottom and on the sides of the sulcus terminalis become more slender and show less distinctive striations when they are embedded in connective tissue. These alterations disappear when the supporting tissue is of the same amount and type as that found in the surrounding myocardium " (p. 397). Certainly the S-A node makes a clear debut at a time long after the heart has commenced to beat in a mature manner. Histological structure cannot, of course, do more than hint at function, but the microscopic appearances of the node are disappointing, to say the least, for the great significance currently attached to it. The significance allotted to the overwhelming nervous tissue in the locality of the node is similarly disappointing (Fig. 26).

The actual origin of the S-A node has long been held to be sinus musculature which persists in the right atrium following the incorporation of the sinus venosus (Keith and Flack, 1906), though the grounds for this belief are by no means clear. Sanabria (1936) points out that once the sinus has been incorporated within the atrium it is impossible to distinguish histologically one from the other. The S-A node develops " . . . dans une région vraisemblablement sinusale, mais il se différencie aux dépens d'une musculature histolgiquement auriculaire " (p. 24). While it may be true that phylogenetically the node is a derivative of the sinus venosus, such an origin is not apparent in ontogeny.

Atrio-ventricular bundle

As indicated above, the localization of the early bundle and its branches suggests that it comes into being along lines of relative inactivity of the myocardium. The intramural Purkinje network, which is prominent in the sheep as well as the ox (Abramson and Margolin, 1935–6), may also be formed in the same way between the primitive trabeculæ whose consolidation goes to make up the great mass of the ventricular wall. Thus Fig. 11 shows early accumulation of glycogen in intertrabecular strands of cells in the depths of the myocardium. Incomplete obliteration of parts of these intertrabecular clefts results in small vessel-like clefts and these have no doubt been responsible for the belief in the especially rich blood supply of the conducting system. The interventricular Purkinje strands described by Wahlin (1927) and again by Abramson and Margolin (1935–6) appear to be of the same origin, since the early interventricular septum can be seen to be made up entirely of loosely packed muscle trabeculæ which gradually become consolidated. As expansion occurs on either side of the septum muscle fibres are orientated longitudinally on the two faces of the septum, and these fibres are from the beginning in continuity with the main stem of the bundle developed on the quiet region below and behind the dorsal endocardial cushion. *No evidence whatsoever of an active growth of bundle tissue either downwards* (Walls, 1947) *or upwards* (Stienon, 1926) *was encountered*, and no especially numerous mitotic or amitotic figures are to be found in the early bundle whose nuclei are rather shrunken and stain deeply. Considered from the phylogenetic standpoint the bundle has been looked upon as a remnant of an earlier and much wider A-V continuity. Benninghof (1923) suggests that the system is a part of the Konturfasern which are more clearly seen in lower hearts. From this inner basketwork of fibres which originally contoured the heart tube, Benninghof derives the trabeculæ of the ventricles, the papillary muscles with their chordæ tendineæ and the heart valves as well as the conducting system. He is of the opinion that the importance of the A-V canal as a special segment of the heart tube from which the conducting bundle is derived, has been exaggerated. He points out that derivation from the canal does nothing to explain the location of the peripheral network, and believes that the main stem of the bundle is a derivative of those Konturfasern which were related to the septum ventriculorum at its appearance in the crocodiles. The present work on the ontogeny of the peripheral network would seem to support derivation from the spongy inner layer of the heart wall (see below).

Some authors maintain that the bundle comes into existence before interruption of the A-V ring takes place (Wahlin, 1935; Shaner, 1929). This precocious appearance has been adduced as evidence of the fundamental significance of the bundle and its importance in the rapidly beating warm-blooded mammalian heart (Davies, 1942). However, the poor differentiation of early connective

tissue makes it difficult to be sure even in complete serial sections at 5μ, that interruption of A-V continuity is complete before the *18-mm.*, though it does seem to be largely accomplished at about the *14-mm. stage*. It would seem then, that (relying on the criteria of orientation and the minimal structural differentiation referred to above) it is possible to identify the bundle before the atria and ventricles become separated by fibrous tissue. Whether this slight anticipation justifies the hypothetical significance accorded it by Davies (1942) is doubtful, especially as the mechanism of relative fixation indicated above would seem to offer a more immediate explanation of the observed appearances.

The system does not, however, differentiate precociously. Even at relatively later stages the bundle may be such a slender structure and so poorly differentiated that its continuity between atria and ventricles may be difficult to follow.

Whether the bundle be regarded as a remnant or as a neomorphic formation, its cells certainly undergo considerable changes in their histological appearances as further development of the heart proceeds in the sheep. Whether these changes are indeed a specialization (which implies a definite function) or whether they are merely a differentiation (in its strict sense) is a moot point. The changes in structure that take place are such as might result from relative inactivity.

Branches of the A-V Bundle

Wahlin (1935) and Sanabria (1936) described consolidation of some of the primitive ventricular trabeculæ to form more or less well-defined columns extending from each face of the upper part of the interventricular septum to the lower part of the lateral wall of the corresponding ventricle and the author's findings confirm these observations.

It is within these columns that the right and left branches of the His bundle are developed, the columns themselves becoming more or less applied to the sides of the septum as ventricular growth takes place. On the right side the lower part of this column is not incorporated within the septum but persists as the moderator band (Fig. 23).

The Peripheral Purkinje Network

The peripheral intramural and subendocardial network arises *in situ* and is derived from the inner trabeculæ layer of the heart wall. A like conclusion has been reached by Stiénon (1925) Sanabria (1936), and Wahlin (1935). Differentiation is earlier in subendocardial fibres than in the depths of the heart wall. There is absolutely no evidence of a progressive peripheral growth of specialized tissue. Phylogenetically, these fibres seem to be related to the Konturfasern of Benninghoff (1923). These fibres are the inner basketwork layer of the heart wall in fishes, amphibians, reptiles, birds, and mammals. Regression of these fibres in higher forms is associated with the development of a well-defined peripheral specialized tissue.

Contrary to what is widely believed, Tawara (1906) was never able to follow microscopically continuity between the branches of the A-V bundle and the peripheral Purkinje network. In attempting this in serially sectioned sheep material, he was defeated by the very complicated nature of the terminal ramifications of the right branch (p. 87) and he met with no more success in the case of the left branch. He goes on " Aber was ich unter dem Mikroskop nicht mehr festellen konnte, konnte ich mit blossem Auge ziemlich gut bei anderen Herzen konstatieren " (p. 94). Tawara assumed that the pale subendocardial network to be seen with the naked eye in the sheep ventricles was the terminal ramification of the bundle branches. Mönckeberg (1908) subjected this assumption of Tawara's to direct examination and concluded that the false tendons of the ventricles sometimes contained no muscle tissue at all or only ordinary muscle. In view of this somewhat unsatisfactory basis for so fundamental an anatomical concept as the conducting system, an attempt was made on the larger hearts of the present series to follow the ramifications of the Purkinje network. In FSH 53 (*100 mm.*) a well defined Purkinje bundle in the moderator band was followed

into the right ventricular wall but the strands of cells quickly dispersed and attempts to link them up were not successful.

The earliest stage at which Purkinje cells may be recognized depends upon the criteria the observer is prepared to accept. Blair and Davies (1935) call attention to the misunderstandings that may arise through loose usage of the term " Purkinje." They stress the view that " continuity with a known part of the conducting system, one or other of the nodes or the A-V bundle or its limbs, is the real criterion of conducting-system fibres, and not peculiarities of histological appearance " (p. 321). Since Tawara, with his vast experience, was unable to adopt this criterion, its use may be regarded merely as a counsel of perfection with little practical importance. It may not, therefore, be out of place to emphasize the essential features of the mature Purkinje cell seen in the new-born lamb heart (Fig. 22).

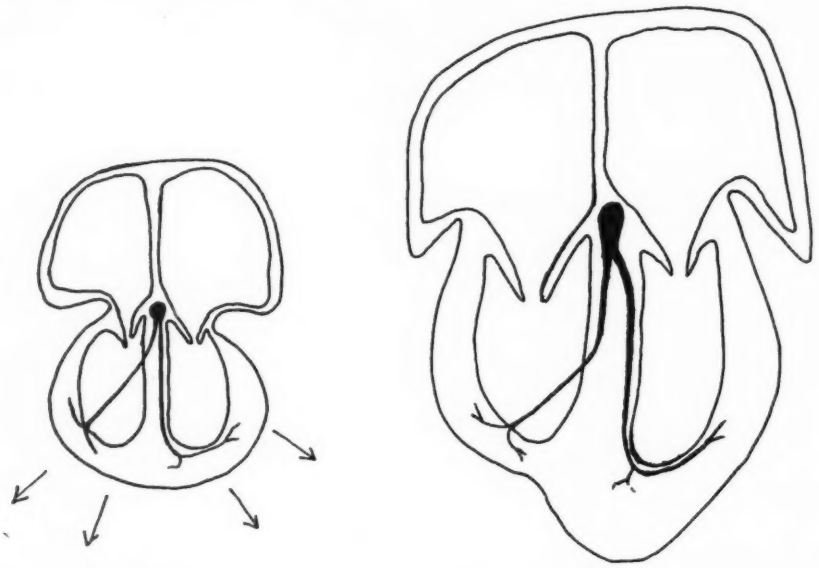

FIG. 23.—(A) Diagram of the conducting system at an early stage. The right branch of the bundle comes off from the interventricular septum at a high level. (B) Definitive condition. Expansion of the ventricles with elongation has taken place, and as a result the right branch of the bundle comes off much lower down from the interventricular septum. Because of the elongation the bundle is less voluminous in relation to its length than it was originally.

Nucleus. Purkinje himself (1845) described each cell as containing one or two nuclei. Ranvier (1875) gave a similar number, whilst Tawara (1906) said that each cell contained one or two nuclei, rarely three. Abramson and Margolin (1935–6) describe the nuclei as multiple. In the present material the author has never seen a Purkinje cell with more than two nuclei. The great majority appear to have two but occasionally there is only one, though this appearance may be due to the plane of section. The nuclei may be close together or may be separated by a distinct interval. Sometimes the appearances suggest strongly that a process of amitotic division has been accomplished. They are rounded and their chromatin granules a little coarser than in the elongated vesicular nuclei of the general myocardium. Surrounding the nuclei is the well-defined perinuclear clear zone containing a little granular material. Most workers regard this space as artificial (cf. Abramson and Margolin, loc. cit.). Nevertheless, a repulsion field seems to exist around the nuclei, for the deviation of the striated fibrillæ from their neighbourhood is a characteristic appearance.

Fibrillæ. These are situated peripherally, well striated, and pass without interruption from cell to cell over long stretches, and in doing so they may pass from one side of the nucleus to the other (Fig. 22).

Cell boundaries. No intercalated discs or other indication of cell boundaries has been seen in the present material (Bouin and alcohol fixed) and the author would agree with those who are of the opinion that Purkinje tissue is of syncytial nature. (Incidentally intercalated discs were conspicuously absent from the general myocardium in all the material examined.) Where many myofibrillæ cross one another some resemblance to an intercalated disc may result, especially as the Purkinje strand is somewhat constricted at this point (Fig. 22).

Connective tissue sheath. The connective tissue sheath has always been looked upon as an important functional component of the conducting system being supposed to act as a sort of insulating mechanism for the cardiac impulse so that it may be carried without lateral spread (" in geschlossenen Bahnen "—Tawara 1906, p. 187). When histological distinction between the ordinary heart muscle and the specialized tissue is poor, this sheath is the one feature that may enable the observer to follow the bundle branches in serial sections. Ontogenetically the sheath appears late, and quite distinct strands of specialized tissue can be found abutting directly on ordinary heart muscle in late embryos, without an intermediary sheath. At these stages the heart has long been beating in apparently mature fashion. On the other hand the fully developed myocardium contains abundant connective tissue fibres readily demonstrable in a good Masson preparation or by silver impregnation. The connective tissue sheath is merely an excess of this tissue in association with the special fasciculi.

Glycogen Content

In general the peripheral parts of the conducting system are richer in glycogen than is ordinary heart muscle, and this richness may direct attention to early specialization which might otherwise escape the eye (cf. Truex and Copenhaver, 1947).

Cells that the writer would assess as distinctly of Purkinje type become recognizable round about the *100-mm. stage*. Sanabria (1936), too, described them at this stage. At birth they are quite mature. As to the mode of multiplication of Purkinje cells, opinions differ. Sanabria (1936), though he admits the existence of many forms suggestive of an amitotic process (cf. his Fig. X, p. 49), thinks that division is mitotic. Bilobed nuclear formations, which he is satisfied are not artefacts, he attributes to amœboid activity. On the other hand, the writer has nowhere seen a mitotic division in a cell that he would regard as of Purkinje type. Sanabria himself does not say he has seen one either; rather he implies the contrary—" cette absence de mitoses n'implique nullement la possibilité des divisions amitotiques " (p. 48). Nowhere has the writer found an illustration of mitotic division in a Purkinje-type cell. While it is impossible to arrive at a firm conclusion on the basis of fixed preparations alone, cells that are to become Purkinje in character seem to multiply by an amitotic process. The great regularity with which one meets two nuclei in each cell and yet the absence of all trace of a mitotic process, coupled with figures strongly suggestive of simple nuclear fission, make this conclusion probable.

Van der Stricht and Todd (1919) are inclined to the same view, and Retzer (1920) strongly so. The question of proliferation of Purkinje cells is important since they have been held to be the source for wear and tear replacement of the myocardium (Hofmann 1902; Retzer 1920). Retzer concludes that the " . . . sino-ventricular bundle (is) primarily a growth centre for the replacement of cardiac musculature. The cells begin their growth in the sinus region of the heart and by a series of direct nuclear divisions eventually reach the sub-endocardial musculature where they pass into cardiac muscle cells." Van der Stricht and Todd (loc. cit) describe Purkinje cells (in the human) as giving rise to ordinary heart muscle cells by longitudinal fission, and this process they saw clearly in diseased hearts where greater replacement demands had to be met. The idea is an attractive one, and is strengthened by the finding of full-blown Purkinje cells (or forms intermediate between them and ordinary heart muscle cells) in the auricles of birds (Holmes, 1923–4) and throughout the auricles

and ventricles in the human (Todd, 1932). In many cases these aberrant conducting fibres are far removed from the location of the conducting system. Nevertheless, the existence of these fibres cannot be lightly dismissed (cf. Davies, 1942) and their occurrence must be taken into account in assessing the function of Purkinje fibres as a whole. This important matter has been reviewed for publication elsewhere. However, the localization of the conducting system to the well-defined bundles in the ungulates is difficult to reconcile with the replacement theory of function. Resistance to the idea that Purkinje cells may have any function other than that of conduction of the cardiac impulse (or indeed, no special function at all), springs from the widely-held belief that conduction by the muscle of the A-V bundle has been conclusively demonstrated. The basis of this belief, which is certainly ill-founded, will be examined elsewhere. Some of the relevant ground has already been covered by Glomset and his collaborators (1940–48) who seek to divest the conducting system of all the properties implied by the name. So far as histological evidence can bear witness as to function, there is nothing about the structure of Purkinje tissue that would lead one to believe in its special conducting powers. On the other hand, the appearance both of the nuclei and of the perinuclear repulsion suggest that an amitotic proliferation may be taking place.

In Fig. 20 a segment of fibres of Purkinje type is shown interposed in the course of a strand of ordinary heart muscle fibres. Ranvier (1875) described similar appearances and Hofmann (1902; Tafel XXVII, Fig. 1 and 2) depicts a like condition. Tawara (loc. cit.) realizing the importance of such an observation from the functional standpoint suggests that Hofmann has committed an error of interpretation and that these appearances are produced by longitudinal section through a right-angled bifurcation of a Purkinje strand. Tawara himself did not encounter such appearances in his own material, and suggests that examination of serial sections might settle the question. However, examination of full serial sections in the author's own material allowed of no certain conclusion. Undoubtedly the occurrence of a segment of Purkinje cells intercalated in the course of an ordinary heart muscle strand is uncommon and Tawara's interpretation may well be correct.

The Relation of Purkinje Fibres to Embryonic Cells

Many eminent histologists have inclined to the opinion that Purkinje cells are embryonic cells of arrested development. Ranvier (1875), Duval (1897), Moriya (1904) among others have all maintained this opinion. A somewhat similar opinion was held by v. Kolliker (1852). He thought the cells were of embryonic character " . . . aber mit Bezug auf die Grösse der Zellen eine eigentümlich entwickelte Form der Muskelfasern des Herzens . . ." (cited by Tawara, 1906). Such an assessment seems altogether reasonable. It does not of course mean that the cells are embryonic but merely that they have been held up in development, have failed to acquire their full complement of striated myofibrils, and have perhaps on this account retained their primitive capacity for multiplication. For Ranvier (1875 " . . . l'interprétation des fibres de Purkinje ne présente aucune difficulté." for " . . . les fibres de Purkinje sont formées par une série de cellules musculaires arrêtées dans leur developpement; elles représenteraient des fibres cardiaques embryonnaires " (p. 538). Equally eminent workers have, however, maintained an opposing view. Gegenbaur (1877) regarded them as specialized cells, though he shows little ground for this belief. Walls (1947) is the latest of a long line of researchers who have followed this authoritative opinion.

Glycogen Content of the Conducting System

The fully developed conducting system has long been known to be rich in glycogen (Marchand, 1885; Mönckeberg, 1908; Aschoff and Nagayo, 1908). These older workers relied largely on the iodine staining and on Best's carmine method (1903) for the demonstration of glycogen. Recently developed histochemical methods would indicate, however, that a considerable variation in glycogen content occurs both in the general myocardium and in the conducting system (Yater *et al.*, 1930) and that excess of glycogen does not in itself constitute a distinguishing feature of the Purkinje cell. Indeed, Buadze and Wertheimer (1928) found by direct chemical estimation that in the horse the

general myocardium contained seven times as much glycogen as the conducting tissue. Truex and Copenhaver (1947) found that Best's carmine staining made positive identification of Purkinje tissue possible in half of their human material. However, these authors observed Purkinje fibres in adjacent sections stained by the azan and Masson methods in cases in which Bests' carmine was entirely negative. The same variability in glycogen—by whatever method adopted for its demonstration—was noted in the present embryonic material, even in specimens of like development and freshness of preservation. Nevertheless, in cases where the general myocardium was relatively rich in glycogen the developing Purkinje tissue stood out well on account of its higher content. The factors that in general influence the demonstrable glycogen, such as the general nutrition of the animal, freshness of specimen, fixative, treatment during dehydration and embedding, would seem to affect equally the content of the general and special myocardium.

Not all parts of the conducting system are equally rich in glycogen. Thus Aschoff and Nagayo (1908), and Mönckeberg (1908) found the A-V node to be free of glycogen. In the present material the glycogen content of the conducting system was found in general to increase from the node distally, the node itself showing little if any excess (cf. Fig. 16 and 17). The final picture of glycogen in the heart can be much modified in intensity by varying the length of differentiation in the methyl-ethyl alcohol mixture. Indeed, more than a perfunctory rinse is often enough to lead to a " glycogen-free " preparation. The intensities of glycogen in Purkinje and ordinary muscle were, however, always parallel. Because of this variability all Best preparations were controlled by the para-periodate method (modified Bauer) carried out on the next slide of the series under standard conditions.

Differences in the glycogen content of the several heart chambers was an occasional finding. Sometimes (Fig. 15) the difference was marked and abrupt under high power examination. Such differences may perhaps reflect different functional states of the heart chambers at the moment of fixation, and in this connection it is interesting that Marcel and Exchaquet (1938) record an example of auricular double rhythm in the human fœtus, the electrocardiographic interpretation being verified by direct observation. Similar differences have been noted in the adult human heart, where the left ventricle may contain more glycogen than the right (Lasch, 1932). Regular variation in glycogen content claimed by Lewis (1925) as between atria, ventricles, and conducting system was not a constant feature in the present material.

The granules of glycogen in both the cells of the general and specified myocardium are often crowded towards one side of the cell. This appearance is probably a fixation artefact, and the same may be said of the numerous extracellular granules that are to be found in most preparations. These findings reinforce the cautionary note sounded by Danielli (1946) with regard to the misleading picture that may result from diffusion phenomena in histochemical techniques.

The very existence of an A-V bundle in the sheep has recently been roundly denied by Glomset, and Glomset (1940). They describe the A-V node as located in the fibrous A-V plate and without connection with the atrial musculature. Whatever may be the state of affairs in the adult sheep. this description certainly does not hold good for the late fœtus, where it is possible to trace the bundle right through from atria to ventricles. However, in the late fœtus the bundle has become so much reduced in size that over long runs of sections one may get the impression that there is no such continuity. But more surprising even than Glomset's denial of the existence of the bundle is the statement (loc. cit. p. 683) " Nowhere did we find any histologic evidence of a change from Purkinje cell to ordinary heart muscle fibre." For such transitions are very common in all older fœtal sheep hearts and have been described by many workers, though some (Marceau, 1902; v. Hessling, 1854) have also found blindly ending ramifications of the Purkinje network. The existence of these latter is difficult to establish with certainty even in complete serial sections, and the writer has found no indisputable examples. Their occurrence would be in accord with the mode of development of the conducting system set out in the above account.

In conclusion, the development of the conducting system is not a spectacular or precocious process. Certainly the embryonic heart is able to beat in the mature fashion and give electrical

recordings comparable in every way with those of the adult long before the special pathway for conduction of the cardiac impulse has been laid down (Marcel and Exchaquet, 1938). Rather the conducting system makes its appearance gradually from cells that by the chance of localization are not concerned with the main work of contraction. These cells do not, naturally, remain quite unchanged whilst all around maturation is proceeding, but, while still retaining obvious embryonic or immature features, develop (in the sheep and other ungulates) well marked characters of their own.

Summary

The atrioventricular bundle can be recognized in a sheep embryo of 7·5 mm. length, provided that orientation of cells rather than histological differentiation be accepted as a criterion. The bundle is recognizable before the A-V node. There is no evidence of an active proliferation of cells to produce the conducting system, nor does there appear to be a migration of cells downwards from the node or upwards from the ventricle. All parts of the system are produced by differentiation *in situ*. The primary location of the A-V bundle along the upper margin of the interventricular septum may be associated with the fact that this region is one of relative rest in cardiac activity. The A-V node arises as a mass of cells that is not caught up in the development of either right or left atrium and therefore retains a somewhat primitive structure. Much the same appearances are shown by cells adjacent to the A-V ring. Neuroblasts appear within the A-V node at about the *50-mm. stage*.

The peripheral Purkinje network arises within the ventricular wall along the lines of intertrabecular clefts which become obliterated as consolidation of the myocardium proceeds. Purkinje fibres are first recognizable about the *100-mm. stage*.

The origin of the peripheral network is in accordance with a phylogenetic derivation from the *Konturfasern* of lower forms.

The system is in many cases distinguishable at an early age of development by its high glycogen content. This may be associated with its formation along planes of relative quiescence in the myocardium.

Differences in the glycogen content of the heart chambers may be apparent, and their significance is briefly discussed.

The sinu-atrial node is a relatively late formation, and appears long after the heart has begun to beat in its adult manner.

Theories of function of the Purkinje network are discussed in the light of histological structure.

I wish to express my gratitude to Professor J. M. Yoffey for his continued interest and encouragement and particularly for making available the technical assistance without which this work would not have been completed. To Professors W. J. Hamilton and J. D. Boyd and the late Sir Joseph Barcroft I am indebted for the loan of valuable material. It is a special pleasure to recall that it was at Professor Hamilton's suggestion that this investigation was undertaken. And, lastly, my thanks are owing to a succession of technical assistants who have helped me in the preparation of so many serial sections. For special mention I would single out Messrs. E. Park, A. E. Westwood, J. E. Hancock, and K. Hunt.

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CONGENITAL ABSENCE OF THE RIGHT BRANCH OF THE BUNDLE OF HIS

BY

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While congenital complete heart block is not very rare, developmental defects of bundle branches are exceptional. In the case here presented the clinical features of congenital heart disease and intraventricular block were found at necropsy to be associated with a congenital absence of the right branch, and it is therefore considered worthy of record.

Case Report

A boy, aged 19 years, was admitted by Professor Henry Moore to the Mater Misericordiæ Hospital, Dublin, on May 8, 1948. Except that he had measles at 10 years of age his previous history was good but his grandmother thought that his face was "inclined to be blueish" when he was six years old; however, his school doctors passed him as fit then and subsequently at 7, 8, and 9 years of age. Nevertheless, he never played games at school. At the age of seventeen he complained that "he was not like other boys of his age, and never seemed to have energy" and that he himself noticed a blue colour of his face. Subsequently, on several occasions he "felt weak" and in one attack sank to the floor for a few seconds but did not lose consciousness. He never complained of tachycardia or dyspnœa. When first seen by us a simple exercise test produced obvious dyspnœa. His face, hands and feet were cyanotic. The heart was conspicuously enlarged to the left and right; there was a slight mitral systolic murmur; the first mitral sound was split (suggesting intraventricular heart block); the aortic and pulmonic second sounds were very faint; the pulse was feeble at the wrist and at rest was 84 a minute. The arterial blood pressure was 104/90. The respiratory rate at rest was 20; the breath sounds at the base of the right lung were diminished and there were crepitations at both lung bases. The urine showed a trace of albumin with an occasional erythrocyte.

A teleradiogram (Fig. 1) showed marked cardiac enlargement, involving especially the right atrium; the ventricular contractions were of diminished amplitude; the inferior vena cava and the pulmonary artery were slightly prominent and the aorta was scarcely discernable; the lungs were radiologically normal and the X-ray diagnosis was congenital heart disease.

The electrocardiogram was of an unusual type (Fig. 2). At first it was thought that it might represent the concordant type of left bundle branch block, but after consideration it was concluded that it indicated an indeterminate form of intraventricular block, with probably lesions in both branches of the bundle of His. Unfortunately, the boy died suddenly, before further unipolar leads had been recorded.

Post-Mortem Examination

An examination of the thorax only was permitted. The heart was fixed in 10 per cent formalin. Sections of the atrioventricular node, bundle, and branches, from other hearts which had previously been prepared by Professor Keenan were used to confirm the findings in this heart. The

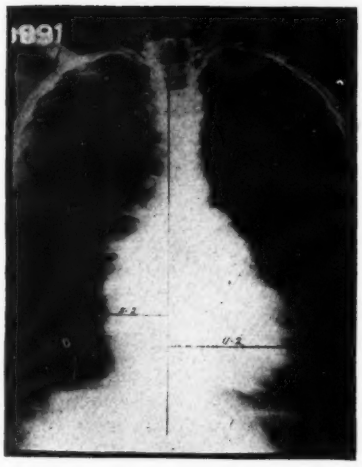

FIG. 1.—Teleradiogram (Dr. J. Geraghty). Measurements: M.R., 5·2 cm.; M.L., 11·2 cm.; M.R.+M.L., 16·4 cm. The diameter of the aortic arch could not be defined.

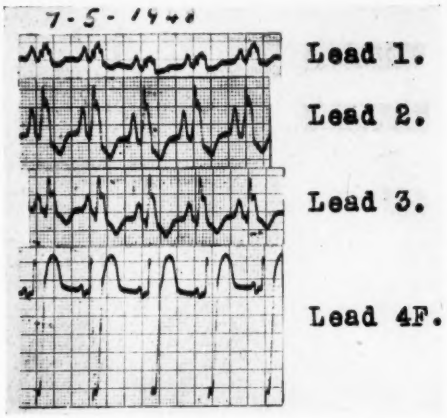

FIG. 2.—Electrocardiogram taken on 7-5-48. Sharp P wave in standard leads, especially in II, and the P–R interval was shortened. QRS shows widening and slurring in all leads. S–T segment abnormal throughout. Appearances suggested indeterminate form of intraventricular block with lesions probably of both bundle branches.

method of serial section of blocks of tissue embedded in paraffin was used throughout. Al sections were cut at a thickness of 10μ and every section was mounted. The sections were stained with a modification of Masson's trichrome stain, using light green.

The Pathological and Anatomical Findings. The heart as a whole was much enlarged and together with the roots of the great vessels weighed 754 grammes. The cavity of the right ventricle was considerably smaller than normal. All the muscle walls were greatly hypertrophied. The aorta was hypoplastic, its diameter at the root of the vessel being 16·5 mm. Dissection of the coronary arteries and their main branches revealed no evidence of occlusion. On section, the right and left coronary arteries and the interventricular branch of the left coronary showed a considerable degree of atherosclerosis, especially the interventricular branch of the left coronary artery.

Microscopic examination of the musculature of the heart revealed a considerable amount of fibrous tissue. This was present particularly between the muscle bundles but also as a replacement fibrosis.

The Conducting System. The sinu-atrial node was sectioned in its entirety and was found to be perfectly normal. The atrioventricular node was also sectioned in its entirety. While not as clearly defined as the sinu-atrial node it was recognized readily enough by its position and the characters of its fibres, and appeared to be perfectly normal.

As the node was traced forwards and to the left, many of the fibres in that portion of it nearest the atrioventricular ring commenced to penetrate the ring (Fig. 3). They constituted the atrioventricular bundle (bundle of His). As it crossed the ring the bundle was embedded in collagenous tissue. Its right border was perfectly clean cut and throughout its course a space, probably an artefact, was observed between that border and the adjacent collagenous tissue (Fig. 3 and 4). All of the conducting fibres in the bundle were cut transversely or slightly obliquely. Those on the right margin of the bundle appeared perfectly healthy and in no way differed from the fibres in the remainder of the bundle. No fibres or portions of fibres emerged from the bundle on its right side.

On reaching the summit of the muscular interventricular septum, the bundle did not divide into right and left branches as occurs in a normal heart. Instead the entire bundle mass was continued into the left branch, passing between the endocardium of the left ventricle and the muscle of the

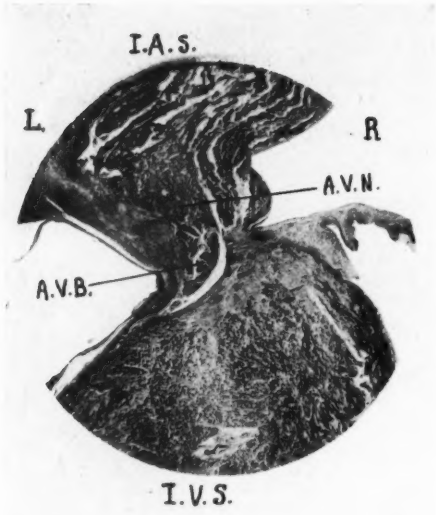

FIG. 3.—Section of the atrioventricular node and proximal portion of the bundle of His. The latter is penetrating the atrioventricular ring. I.A.S., interatrial septum; I.V.S., interventricular septum; A.V.N., atrioventricular node; A.V.B., atrioventricular bundle. Magnification, ×24.

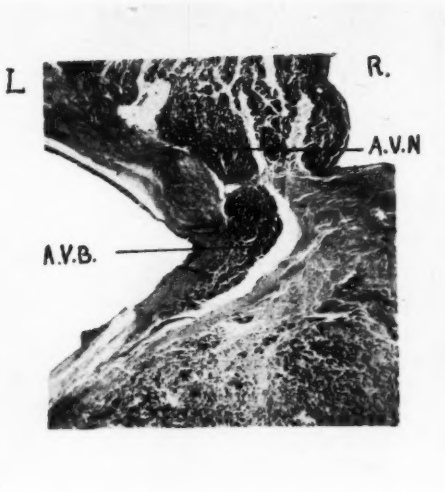

FIG. 4.—Section further forward than in Fig. 3. Showing the atrioventricular node (A.V.N.) and atrioventricular bundle (A.V.B.). Magnification, ×24.

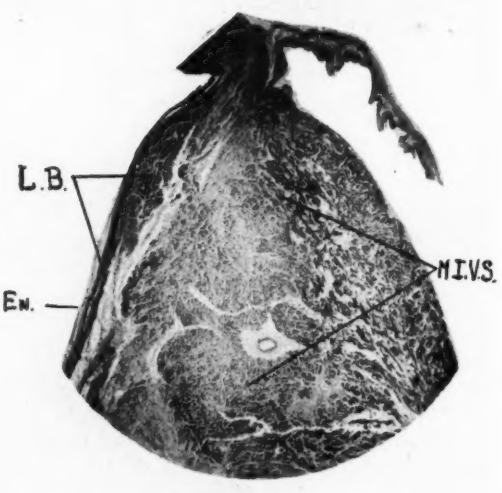

FIG. 5.—Section further forward than in Fig. 4, showing longitudinally cut fibres of the left branch (L.B.) passing towards the apex of the heart and lying directly under the endocardium of the left ventricle (En.). M.I.V.S., muscular interventricular septum. Magnification, ×8.

interventricular septum. A number of fibres emerged from this left branch, one or two at a time, and immediately joined with the muscle of the septum on its left side whence they could not be traced any further. The remaining fibres of the branch passed towards the apex of the heart, directly beneath the endocardium of the left ventricle (Fig. 5). These fibres formed a broad, flattened band, which became condensed into four main divisions. A few fibres passed from these four divisions and immediately joined with the muscle of the septum whence they could not be traced any further.

Approximately 1–1½ inches below the summit of the muscular interventricular septum the anterior three of these divisions showed fibrous lesions. Here the conducting fibres were stained more palely than the adjacent muscle of the septum; their cell outlines were indistinct and the protoplasm was beaded in appearance. In these three divisions the conducting tissue was replaced by fibrous tissue and the continuity completely interrupted. These fibrous lesions were probably ischæmic in origin. Below the lesions, conducting fibres were again present and they were traced towards the apex of the ventricle. Each of the three divisions was interrupted by a second fibrous lesion. No attempt was made to trace them any further.

The fourth and most posterior division of the left branch of the bundle of His gave a branch that formed a trabeculum in the cavity of the ventricle, a portion of which unfortunately was destroyed when blood clot was being removed from the ventricle. Shortly after, this division was also completely interrupted by a fibrous lesion. Conducting fibres were present below the lesion and they were traced to the apex of the ventricle, where they were distributed to the adjacent heart muscle. In the lower portion of its course this division formed a strand which lay free in the cavity of the ventricle.

Thus all the fibres of the bundle of His that had crossed the ring from the atrioventricular node had run into the left branch. No right branch was present in this heart nor were there any conducting fibres going to the muscle of the septum on its right side.

Discussion

The possibility of a lesion in the right branch at the bifurcation of the bundle was considered. Had there been such a lesion, we think that at least a few damaged fibres would have been present to indicate the position of a right branch. No such fibres were present and there was no evidence in the sections to indicate a lesion. Further, the pathway that the right branch normally follows was sectioned down to and including a portion of the moderator band. The absence of the right branch in that pathway, in this heart, was supported by demonstration of its existence in similar sections prepared from other hearts. Sections from another heart, reported by Moore, Keenan, and Moriarty (1937) revealed a lesion in the right branch and below this lesion conducting fibres were again present in an apparently healthy condition. Similarly, in the heart now under consideration, healthy conducting fibres were observed below the lesions in the left branch; had there been a lesion high in the right branch, then healthy fibres would be expected below it, in the normal pathway of the branch. No such fibres were present in this heart.

A lesion in the right branch, at the bifurcation of the bundle, many years before the patient's death, might possibly produce the condition found in this heart. This would necessitate the complete obliteration of all right branch fibres in the region of the lesion. It would also necessitate that any healthy fibres, distal to the lesion, would have been widely separated from the bifurcation of the bundle by the enlargement of the heart. It is felt that even with such a lesion some remnants of fibres would still be present, certainly at the bifurcation of the bundle. It is very doubtful if these circumstances could result in the perfectly clear cut and healthy right border of the bundle that was found in this heart. Further, there should be some, and possibly a considerable amount of, fibrous tissue in the normal pathway of the right branch. In fact, this portion of the septum was remarkably free of fibrous tissue (Fig. 5). Such a lesion, with the sequelæ mentioned, is considered extremely unlikely to have been present in this heart.

Examination of the atrioventricular node and the regions beyond each of its ends revealed no conducting fibres crossing the ring independent of the bundle of His. Further, no bundle of Kent was found in this heart, though a very thorough search was made for fibres crossing the atrioventricular ring from the right atrium to the right ventricle. Almost the complete ring was sectioned in this portion of the heart.

We conclude, therefore, that the absence of the right branch of the bundle in this heart must be due to a congenital defect. The work of Walls (1947) may serve to explain the congenital absence of the right branch in this heart, combined with a developmentally normal bundle and left branch; he states that the atrioventricular node represents part of the wall of the atrioventricular canal and that the bundle of His and its branches are a new formation, which arises by a process of active growth from the primitive nodal tissue. Theoretically, then, any disturbance of this growth could result in the absence of either or both of the branches. Indeed, it seems feasible that the bundle itself might fail to grow. Walls also states that the bundle and the commencement of the left branch are present at an earlier stage in development than the right. Consequently they could be perfectly normal structurally in the adult heart, even if the right branch had failed to develop. Further, the downward growth of the bundle and its branches, combined with the upward growth of the summit of the interventricular septum, could facilitate the failure of development of a branch by isolating the downwardly growing structure to one side.

I am indebted to Professor Henry Moore, at whose instigation the work was carried out, for helpful advice and assistance, and also to Professor Edward Keenan for the same reasons and for allowing the work to be done in the Anatomy Department of University College. My thanks are due to Dr. M. D. Hickey for his generous advice on the pathological features of the heart. I am also indebted to the Medical Research Council of Ireland for a grant which enabled the work to be carried out; to Dr. S. O'Carroll of Dromhair for information as to the history of the case; and to Mr. R. Kernan and Mr. P. Fletcher for valuable technical assistance.

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THE PHONOCARDIOGRAM OF AORTIC STENOSIS

BY

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From the Cardiac Department of the London Hospital

Received May 1, 1950

Aortic stenosis produces a systolic murmur of characteristic shape in the phonocardiogram both in the aortic and mitral areas. Sound records were taken in 20 patients with aortic stenosis. The phonocardiograph used for this investigation has been described elsewhere (Leatham, 1949), and consisted of crystal microphones, valve amplifiers, and both string and mirror galvanometers. Filters were used to reduce the intensity of the low frequencies to about the same extent as effected by the human hearing mechanism; the resulting curve is called high frequency or logarithmic (Rappaport and Sprague, 1941). Records from the aortic and mitral areas were often made simultaneously. In each patient there was good clinical evidence of aortic stenosis and in 13 of them calcification of the aortic valve was seen on fluoroscopy. Any patient with a mitral diastolic murmur, whether audible or recorded by the phonocardiograph, or with radiological evidence of left auricular enlargement was excluded from the series.

The onset, shape, and termination of the systolic murmurs in these patients are represented by the diagram in Fig. 1, and phonocardiograms are shown in Fig. 2 to 6. The exact moment of onset of a systolic murmur is difficult to determine for it may be confused with high frequency components of the first sound, but appeared to start immediately after the first sound in some or later in others, as pointed out by Evans (1947). In 19 of the 20 cases in the present investigation the vibrations were small at first, rose to a peak in mid-systole, and then diminished in size until they were small or absent before the second sound; in one subject (Case 10) the accentuation was earlier in systole. This symmetrical pattern with mid-systolic accentuation was usually best seen in the aortic area, but was always present in the mitral area too. A second sound was always recorded though in some it may have been pulmonary in origin. A diastolic murmur following the second sound was heard and recorded in 13 subjects. An aortic systolic murmur of the shape described does not occur in stenosis only, for it is found in aortic sclerosis, coarctation of the aorta, and syphilitic aortic incompetence (Fig. 7).

The systolic murmur of mitral valve disease was found to be of different shape. It usually started immediately after the first sound and continued to the second sound with no sharp mid-systolic accentuation (Fig. 8 and 9). In some patients with mitral incompetence the murmur was mainly in late systole.

In pulmonary stenosis the systolic murmur was usually different from that in aortic stenosis. There was less mid-systolic accentuation and the murmur extended to the second sound or beyond it (Fig. 10).

Discussion

It is known that the systolic murmur of aortic stenosis may be loud at the mitral area and even louder here than in the aortic area. Graphically, the murmur is the same in both areas, emphasizing the good conduction of sound from the aortic valve to the mitral area. When a systolic murmur is

louder at the mitral area than at the aortic area, as it was thrice in this series, mitral valve disease may be suspected, but the phonocardiogram can differentiate the two.

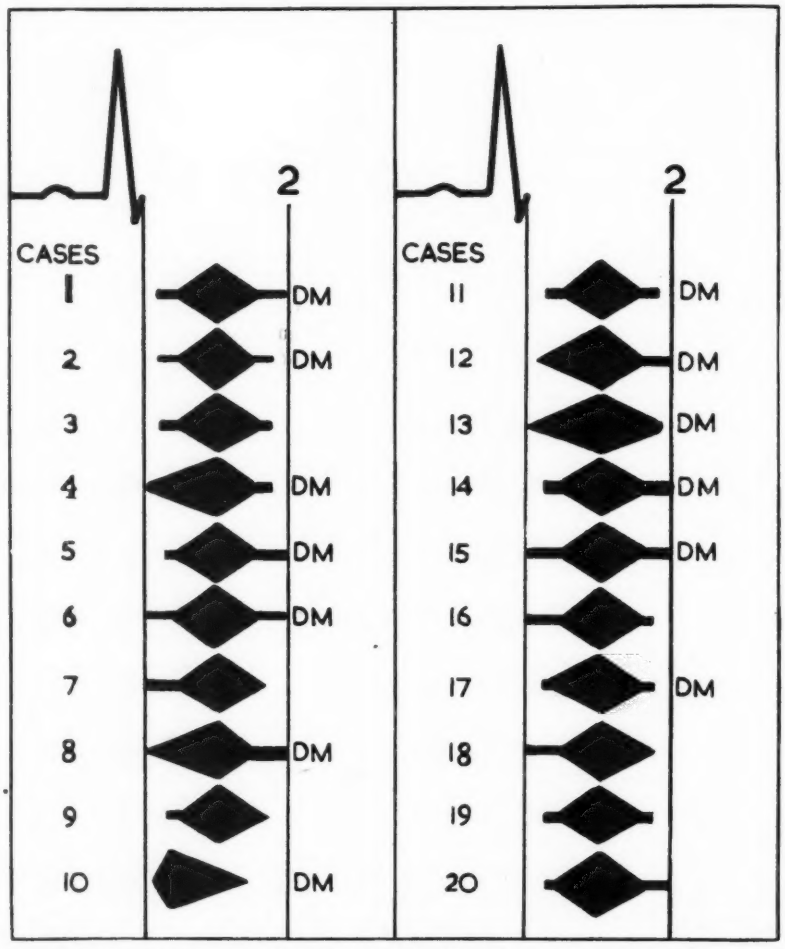

FIG. 1.—Diagram showing the murmurs of aortic stenosis in 20 patients. The systolic murmur is related to the electrocardiogram and to the second heart sound. There is an aortic diastolic murmur (DM) in 13 patients.

It is strange that there is usually a difference between the systolic murmurs of aortic and pulmonary stenosis. In the phonocardiogram of a patient with pulmonary stenosis (Fig. 10) the second sound recorded at the mitral area is probably aortic in origin. The systolic murmur in the pulmonary area reaches this second sound and extends beyond it into diastole. This might be regarded as a pulmonary diastolic murmur. Another explanation is delay in termination of right ventricular systole and continuation of the pulmonary systolic murmur beyond the aortic second sound. This murmur might finish before a late pulmonary second sound which would then bear the same relation to a pulmonary systolic murmur as the aortic second sound and systolic murmur in aortic stenosis. Unfortunately a pulmonary second sound can seldom be demonstrated in pulmonary stenosis.

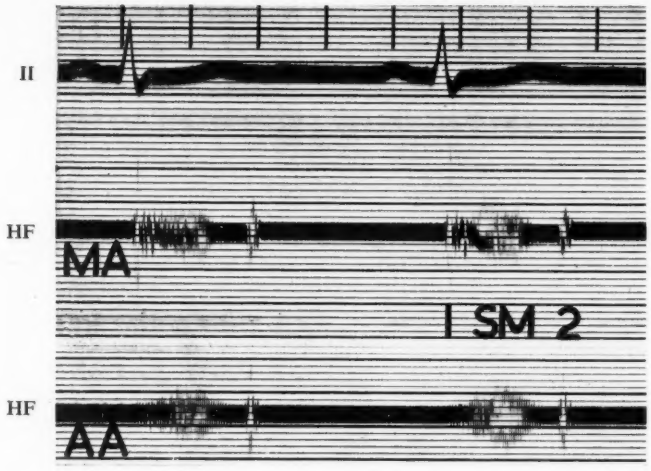

FIG. 2.—Aortic stenosis. The systolic murmur starts soon after the first sound, rises to a peak about mid-systole, and diminishes before the second sound. The murmur has the same shape in synchronous high frequency records (HF) from the mitral area (MA) and aortic area (AA). The time interval in this and subsequent records is 1/5 sec.

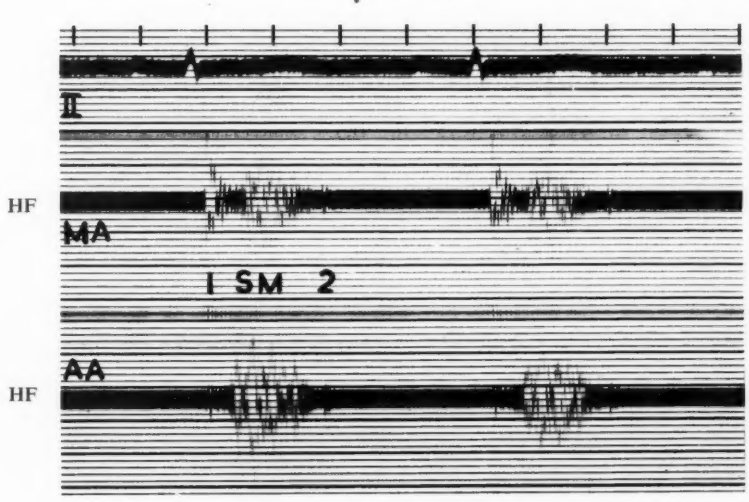

FIG. 3.—Aortic stenosis (see Fig. 2).

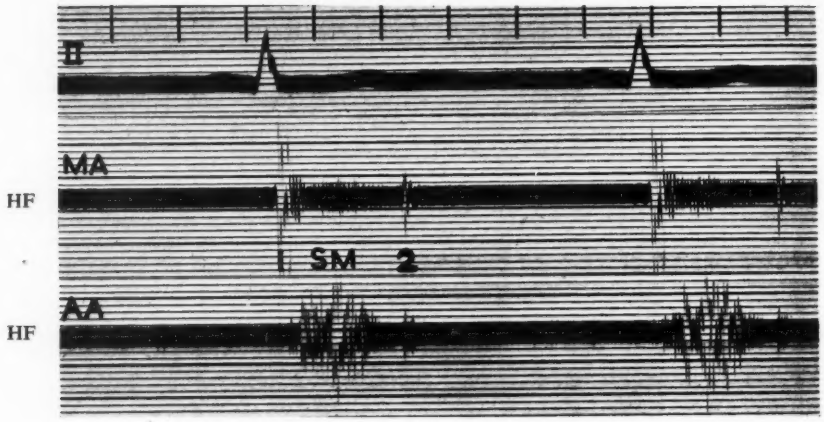

FIG. 4.—Aortic stenosis.

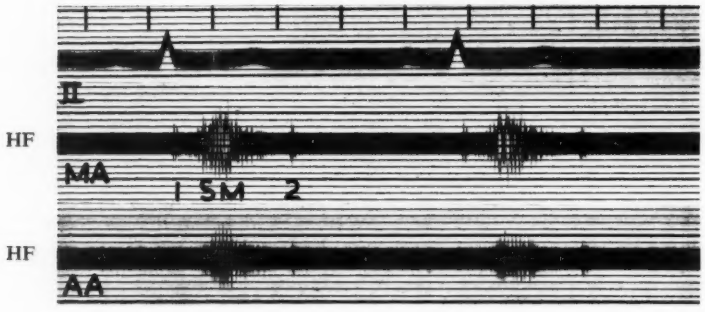

FIG. 5.—Aortic stenosis.

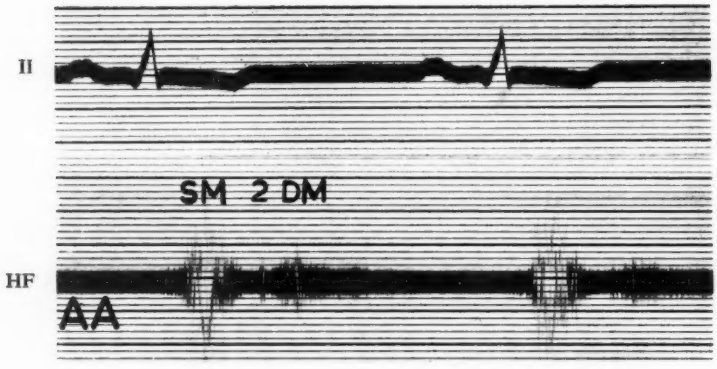

FIG. 6.—Aortic stenosis and incompetence.

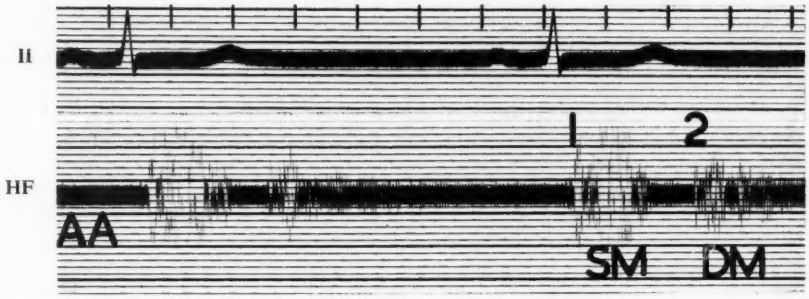

FIG. 7.—Syphilitic aortic incompetence. The systolic murmur has the same shape as in aortic stenosis.

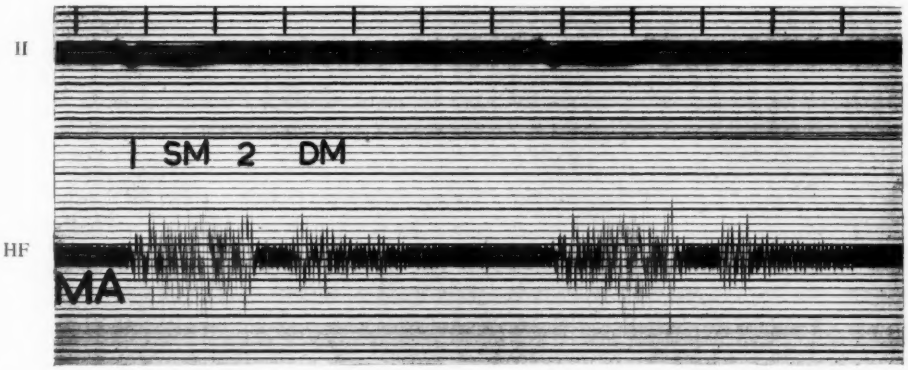

FIG. 8.—Mitral valve disease with auricular fibrillation. The systolic murmur fills systole between the first and second sounds. There is a mitral diastolic murmur (DM).

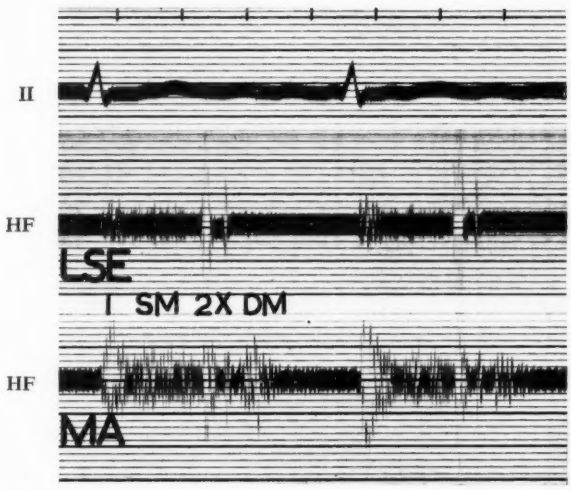

FIG. 9.—Mitral valve disease with auricular fibrillation. The systolic murmur fills systole. There is an "opening snap" (X) loudest at the lower left sternal edge (LSE), and a mitral diastolic murmur.

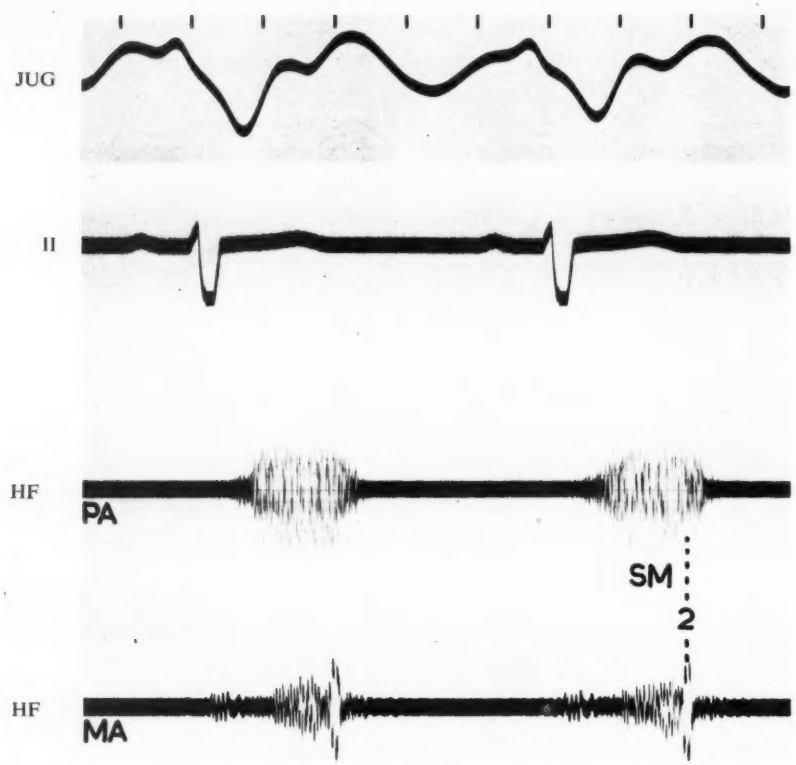

FIG. 10.—Pulmonary stenosis. The murmur in the pulmonary area (PA) extends beyond the second sound recorded at the apex (MA).

CONCLUSION

The phonocardiogram of aortic stenosis shows a systolic murmur of characteristic shape both in the aortic and mitral areas. The murmur is small at first, rising to a peak in mid-systole and then decreasing so that it is small or absent before reaching the second sound. In mitral valve disease the systolic murmur tends to fill systole more evenly or to be mainly in late systole, while in pulmonary stenosis the systolic murmur usually extends to the second sound.

NOTE: Since this communication was given to the British Cardiac Society in June, 1949, Dr. S. A. Levine in "Clinical Auscultation of the Heart" (W. B. Saunders Co., Philadelphia and London, 1949) has described the systolic murmur of aortic stenosis as of diamond shape in the phonocardiogram. He writes that "The form of the sound tracing has been so constant that we have wondered whether it might be helpful diagnostically. It appears that the systolic murmur of mitral insufficiency, from which it needs to be differentiated, takes on a different form, having a plateau, diminuendo, or crescendo configuration."

I wish to thank Sir John Parkinson and Dr. William Evans for much helpful advice and encouragement, and Mr. William Dicks for his co-operation in making the recordings.

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THE ELECTROCARDIOGRAM ASSOCIATED WITH LOW LEVELS OF SERUM POTASSIUM

BY

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Received May 7, 1950

In recent years it has become increasingly evident that a depletion of body potassium may occur in a number of conditions. The relationship of a fall in the serum potassium to the attacks of familial periodic paralysis is well known. Potassium deficiency has also been found in infantile diarrhœa, intestinal obstruction with vomiting, sprue, renal insufficiency, diabetic coma, Addison's disease with overdosage of desoxycorticosterone acetate, and in patients in whom the potassium intake has been low over a long period. Abnormalities in the electrocardiogram have been reported in each of the above conditions when the serum potassium has been at a low level. These abnormalities have been found mainly in the S–T segment, the T wave, and the Q–T interval. Electrocardiograms of three cases with low serum potassium are presented in this paper; in two of them it remained low over long periods and many tracings were obtained.

PROCEDURE

All the serum potassium estimations were made by a modification of the method of Kramer and Tisdall (Jacobs and Hoffman, 1931) using a photo-electric absorptiometer for evaluation of the colour. Special precautions were taken to prevent hæmolysis on withdrawal of the blood and the serum was removed within two hours of collection. The accuracy of the method, using duplicate estimations, was found to be $\pm 0{\cdot}5$ mg. per 100 ml. Normal values by this method lie between 16 and 20 mg. per 100 ml. of serum.

Electrocardiograph leads I, II, III, V1, V3, and V5 were used. All tracings were taken with the patient recumbent. Care was taken to exclude, as far as possible, factors other than potassium that might influence the S–T segment or the T wave. In no case was there evidence of coronary disease, preponderance of a ventricle, paroxysmal tachycardia, severe anæmia, myxœdema, tetany, or trauma to the chest wall. No digitalis or other significant drugs had been given. In all tracings, the Q–T interval measurement was corrected for the heart rate using Bazett's formula as expressed by Taran and Szilagyi (1947) where $K = \frac{Q\text{–}T}{\sqrt{C}}$ [C = cycle length; K = the corrected Q–T interval].

On every occasion, the electrocardiogram and the blood sample were taken simultaneously. This was considered essential as the serum potassium level is known to vary from hour to hour, especially when the patient is being given potassium salts (Wilkins and Kramer, 1923; Sampson *et al.*, 1943). Forty-four cardiograms corresponding to various levels of serum potassium were studied in the three cases.

CASE REPORTS

Case 1. Woman, aged 41 years. A typical case of idiopathic steatorrhœa admitted during an acute phase of the disease. The patient was thin and poorly developed. The tongue was smooth and there were fissures at the angles of the mouth but there were no other abnormal physical signs. The blood pressure was 105/80. Radiological examination showed a normal,

small heart and clear lung fields. Blood chemistry values per 100 ml. of serum were: sodium 317 mg., potassium 10·4 mg., calcium 9·2 mg., and chlorides (as sodium chloride) 654 mg.

The patient's serum potassium remained low for the first three months under observation. Subsequently, as her condition improved, the level rose to 20·6 mg. per 100 ml. The blood chemistry was otherwise always normal. With the alterations in the serum potassium there was at no time any significant change in the state of the cardiovascular system.

Electrocardiograms. During the whole period of observation a series of cardiograms was taken which covered a range of serum potassium levels from 20·6 mg. to 12·1 mg. per 100 ml. (Fig. 1). In this series, all tracings taken at levels above 18·3 mg. per 100 ml. are normal, whereas, at and below this level they show an abnormally flat or inverted T wave and sometimes a depressed

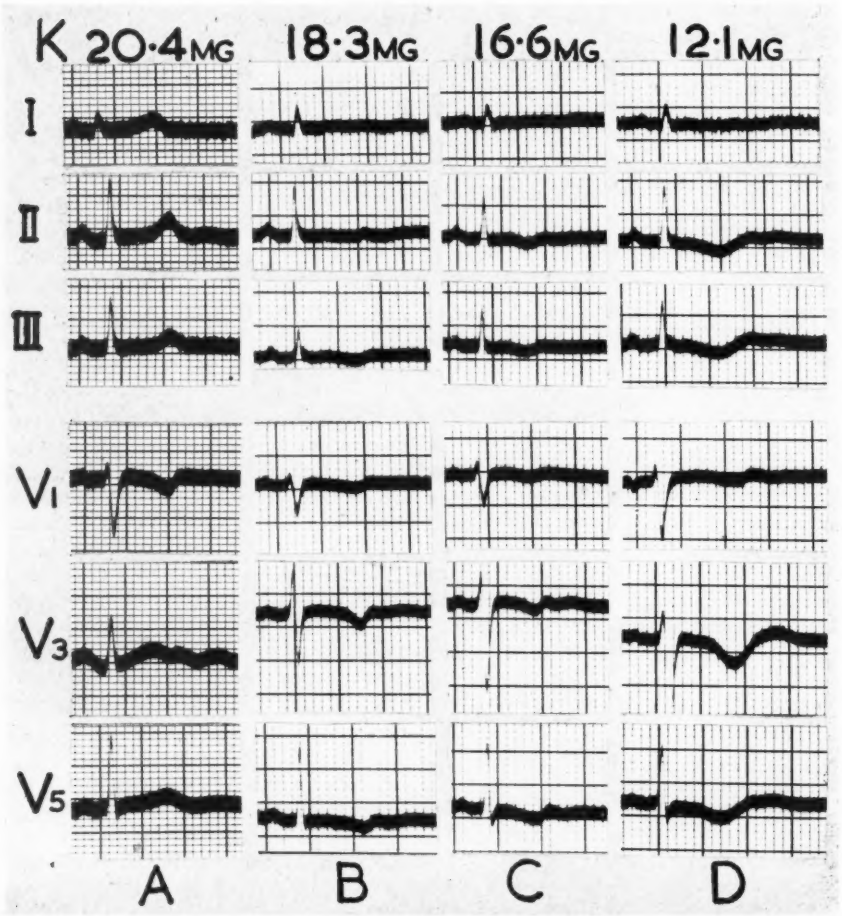

FIG. 1.—Case 1. Tracings at different levels of serum potassium: (A) Normal tracings. The Q–Tc is 0·411 sec. As the serum potassium falls (B) the T wave becomes abnormally flat in leads I and II, and inverted in III, V3 and V5. The Q–Tc is 0·400 sec. (C) The T wave is now also inverted in lead II and the S–T segment is slightly depressed in V5. The Q–Tc is 0·400 sec. (D) The abnormalities in the T wave and the S–T segment are more marked. Normal U waves are now visible in most leads. The Q–Tc is 0·402 sec.

S–T segment. Both the degree of the abnormalities and the number of leads in which they are seen, increase in proportion to the fall of the serum potassium. The electrocardiograms are normal in all other respects.

The corrected Q–T interval has a range from 0·402 to 0·426 sec. The slight variations in the Q–T interval are unrelated to the level of the serum potassium. Abnormalities are present in the electrocardiograms of this case even when the serum potassium is within the usually accepted limits of normal. The abnormalities in the electrocardiogram could be corrected temporarily by giving potassium chloride intravenously (Fig. 2).

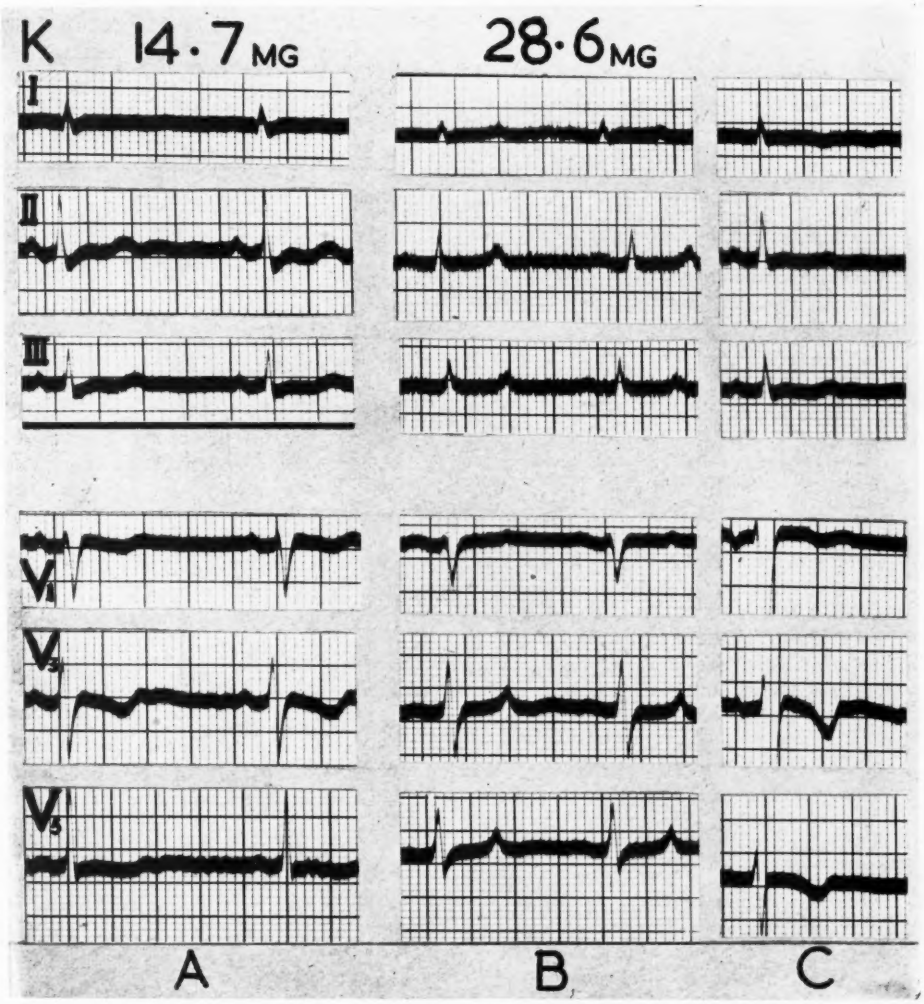

FIG. 2.—Case 1. The effect of intravenous potassium chloride on the electrocardiogram; 10 g. of potassium chloride were given over a period of two hours. (A) Before potassium. The S–T segment is depressed in leads II, III and V5; the T wave is flat in leads I and V5, and inverted in V3. (B) At the end of the two hours of intravenous potassium. The abnormalities have been corrected. (C) Seventy-two hours after (B); the T wave is again flat in lead I and inverted in V3 and V5.

Case 2. Woman, aged 39 years. A known case of ulcerative colitis of three years duration who was admitted to hospital during an exacerbation of her disease. The patient was thin but there were no abnormal physical signs in any system. The blood pressure was 120/70. Radiological examination of the heart and lungs was normal. The blood chemistry values per 100 ml. of serum were: sodium 311 mg., potassium 16·1 mg., chlorides (as sodium chloride) 555 mg., calcium 8·4 mg., and phosphorus 4·6 mg. Two subsequent serum potassium determinations showed levels of 12·9 and 18·0 mg. per 100 ml.

Electrocardiograms (Fig. 3). As the serum potassium level falls there is some decrease in the amplitude of the T wave in the chest leads. However, the T wave and all other parts of the tracing are within normal limits. The duration of the corrected Q–T interval is almost constant throughout.

Case 3. Woman, aged 45 years. A case of ulcerative colitis of more than twenty years duration. The right kidney had been removed for an abscess ten years previously. She was admitted because of increasing severity of her bowel condition. The patient was thin, but there were no abnormal physical signs to be found in any system. The blood pressure was 110/70. An X-ray of the chest showed a normal, small heart and clear lung fields. The renal function tests were normal. Blood chemistry values per 100 ml. of serum were: sodium 304 mg., potassium 11·1 mg., chlorides (as sodium chloride) 590 mg., calcium 11·6 mg., and phosphorus 3·7 mg. Subsequent determinations showed no significant change from normal other than in the serum potassium.

The diarrhœa was unremitting for the next twelve months and during this time the patient was liable to attacks of severe muscular weakness which coincided with very low serum potassium levels. These attacks were relieved by giving potassium chloride by mouth. Throughout the whole of this time the serum potassium remained at an abnormally low level unless the patient was given potassium.

Electrocardiograms. A series of cardiograms was obtained on this patient at 27 different levels of the serum potassium. The range was from 21·0 to 6·3 mg. per 100 ml. (Fig 4 and 5). In this series, all tracings at levels above 11·9 mg. per 100 ml. are within normal limits. At and below this level they show a depressed S–T segment, an abnormally low or inverted T wave and a large U wave (Fig. 4C). Both the degree of the abnormalities and the number of leads in which they are present, increase in proportion to the fall of the serum potassium. At the lowest serum potassium levels, a characteristic undulating tracing is produced by the deep depression of the S–T segment, the flat or inverted T wave, and the grossly high and wide U wave (Fig. 5).

In some of the tracings at the lowest serum potassium levels, the height of the P wave in lead II is greater than 2·5 mm. and the duration of the QRS complex is at the upper limit of normal. The corrected Q–T interval has a range from 0·402 to 0·442 sec. Its variations are unrelated to the level of the serum potassium. It is of interest to follow the changes that occur in the T wave and the U wave as the serum potassium falls. These changes are most clearly seen in lead V3 (Fig. 6). The T wave steadily decreases in amplitude, becomes flat and then inverted. Concurrently, the U wave increases in height and width and encroaches upon the T wave. Difficulty may arise in the interpretation of the tracing when the T wave is flat and the U wave is high. Here, the U wave may easily be mistaken for an upright T wave associated with a prolonged Q–T interval (Fig. 5 and 6). The true nature of this U wave is usually revealed by the presence of an upright or inverted T wave preceding it in one of the other leads (Fig. 5).

It was found that all the abnormalities in the cardiogram could be corrected within one hour by the administration of 7·5 g. of potassium chloride by mouth. Four hours after this dose the cardiogram reverted to its previous state.

Comment

Each of the three cases reported has a different response to a fall in the serum potassium as shown in the electrocardiogram. This is well seen at levels in the region of 12 mg. per 100 ml. In Case 1, S–T segment depression and T wave inversion occur. In Case 2, there is lowering of the

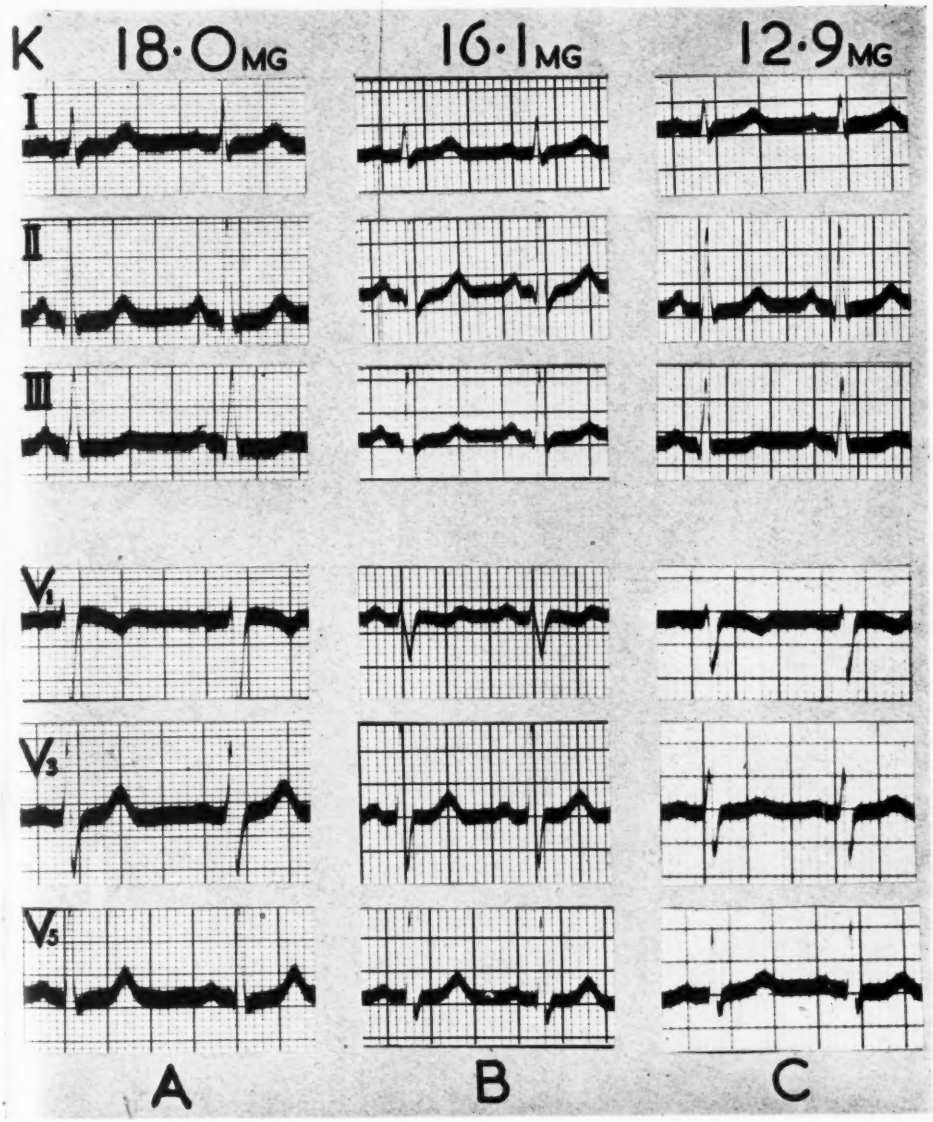

FIG. 3.—Case 2. Tracings at different levels of serum potassium. There are no abnormalities to be seen, but as the potassium falls there is some reduction in the amplitude of the T wave in leads V3 and V5. The Q–Tc is in (A) 0·418 sec., in (B) 0·400 sec., and in (C) 0·410 sec.

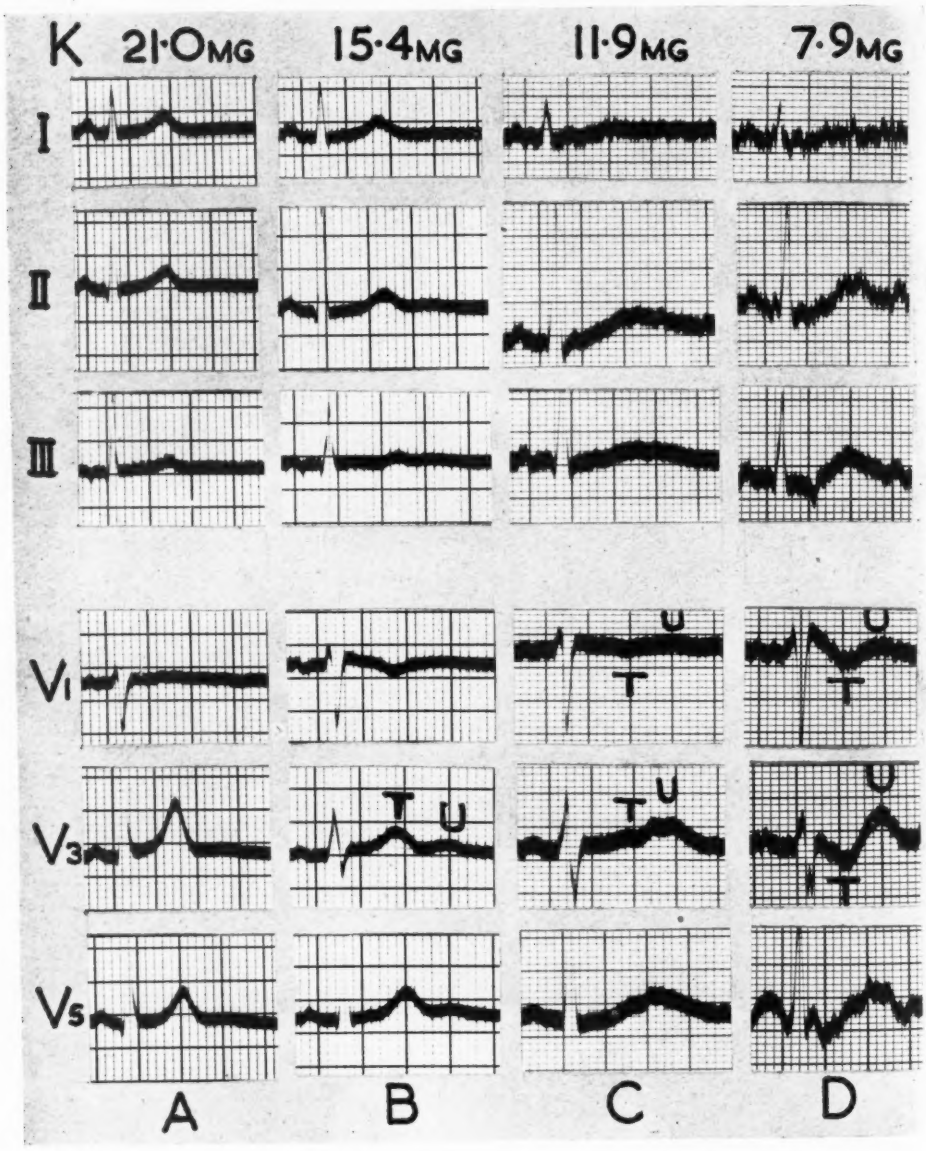

FIG. 4.—Case 3. Tracings at different levels of serum potassium. (A) Normal tracings. Q–Tc is 0·400 sec. (B) Normal tracings, but there are some changes in the amplitude of the T wave and the U wave. The Q–Tc is 0·420 sec. (C) In leads II, III, V3 and V5, the T wave is of low amplitude and the U wave is large. In lead II and V5 there is slight S–T segment depression. The Q–Tc is 0·416 sec. (D) In leads III, V3, and V5 the T wave has become inverted. The abnormalities in the S–T segment and the U wave are greater. The Q–Tc is 0·400 sec.

T wave voltage only. In Case 3, a depressed S–T segment is combined with a low T wave and a large U wave. Further, in Cases 1 and 3, there is a marked difference in the level to which the potassium falls before the electrocardiogram becomes abnormal (18·3 and 11·9 mg. per 100 ml. respectively).

In Case 3, when the serum potassium is low, there is an abnormal increase in the amplitude of the P wave. This is in contrast to the flattening or disappearance of the P wave which is known to be associated with a high level of serum potassium. In none of the three cases is there lengthening of the Q–T interval with a fall in the serum potassium.

Previously Reported Cases

Electrocardiograms associated with low serum potassium levels have been presented in reports on familial periodic paralysis (Stewart *et al.*, 1940; Stoll and Nisnewitz, 1941; Gass *et al.*, 1948; Perelson and Cosby, 1949), infantile diarrhœa (Gamble *et al.*, 1948), intestinal obstruction (Bellet *et al.*, 1949), sprue (Engel *et al.*, 1949), renal insufficiency (Brown *et al.*, 1944; Tarail, 1948), diabetic coma (Holler, 1946; Martin and Wertman, 1947; Nadler *et al.*, 1948; Ernstene and Proudfit, 1949), Addison's disease (Thompson, 1939; Currens and White, 1944; Ernstene and Proudfit, 1949), and various conditions with a low potassium intake (Tarail, 1949).

In most reported cases, the period of low serum potassium was brief and few electrocardiograms could be obtained. In a number of cases the cardiogram and serum potassium recording were not simultaneous, being separated sometimes by as long as 24 hours. It is therefore difficult to establish the potassium level at which abnormalities appear in the electrocardiogram, and also to appreciate the progression of these abnormalities as the level falls.

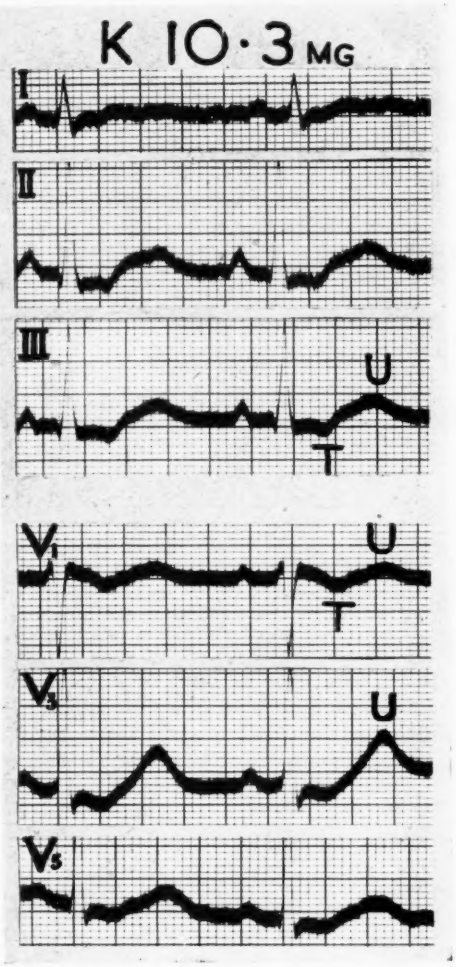

FIG. 5.—Case 3. The electrocardiogram at a serum potassium level of 10·3 mg. per 100 ml. In leads II, III, V3 and V5, the S–T segment is depressed, the T wave is flat or inverted, and the U wave is abnormally high and wide. Lead V1 clearly shows an inverted T wave and an upright U wave. In lead II the height of the P wave is more than 2·5 mm. The duration of the QRS complex is 0·10 sec.

In a number of reports, where the Q–T interval is said to be prolonged (Stewart *et al.*, Ernstene and Proudfit, Perelson and Cosby, and Engel *et al.*), broad and deformed T waves are described. These waves are similar in form and position to the U waves of Case 3 in this paper, and they are part of a similar undulating outline. That these broad waves are in fact U waves is confirmed by the presence of preceding small T waves in some of the leads. It is considered, therefore, that the Q–T interval has been over-estimated by these authors and is actually within normal limits in most of their cases. The only reported case with a high voltage P wave at low levels of potassium was Case 6 of Ernstene and Proudfit.

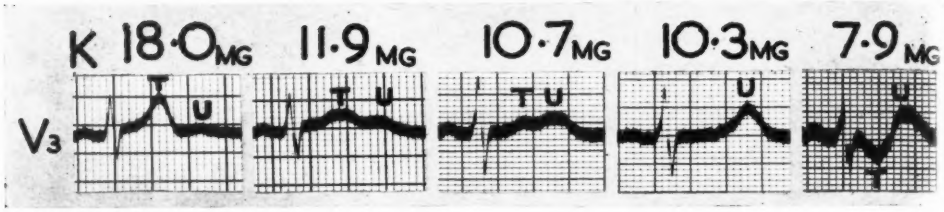

FIG. 6.—Case 3. Lead V3 showing the change in the T wave and the U wave as the serum potassium falls. The T wave decreases in amplitude and eventually becomes inverted; at the same time the U wave increases in amplitude and width. At 10·3 mg. per 100 ml. the U wave simulates an upright T wave associated with a prolonged Q–T interval.

SUMMARY AND CONCLUSIONS

The abnormalities in the electrocardiogram associated with low serum potassium were studied in three cases. A different type of tracing was found in each case. The level of serum potassium at which abnormalities first appeared was determined in two of the cases.

On examination of the tracings of these cases and of those previously reported, it is found that a lowering of the serum potassium may result in changes in almost any part of the electrocardiogram. Decrease in the amplitude of the T wave is constant and may proceed to inversion. Depression of the S–T segment is frequent. Marked increase in the size of the U wave occurs in less than half of the cases. Lengthening of any part of the electrical cycle may occur. High voltage of the P wave may be present occasionally.

The above abnormalities may be combined in various ways. In most cases, the resultant tracing has no characteristic form. In some cases it has an undulating outline produced by a depressed S–T segment, a low or inverted T wave, and a high and wide U wave. This outline is strongly suggestive of low serum potassium and may prove to be diagnostic. No one type of tracing was found to be constantly associated with any one causative disease or condition.

It is considered, contrary to most previous reports, that a prolongation of the Q–T interval is not commonly associated with a fall in the serum potassium.

I wish to thank Dr. N. F. Coghill for permission to study his cases and for his encouragement in the preparation of this paper. I am indebted to Dr. M. Lubran for much helpful criticism. I also wish to thank Mr. R. J. Hall for the many biochemical estimations, and the staff of the Electrocardiographic Department for their kind co-operation.

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COLD AND WARMTH VASOCONSTRICTOR RESPONSES IN THE SKIN OF MAN

BY

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The increase in peripheral blood flow that follows the application of heat to the body is brought about in part by a purely nervous mechanism initiated in the skin, and in part by the central action of circulating warmed blood (Pickering, 1932). The author has recently analysed in detail the separate parts played in peripheral vasodilatation by rising environmental temperatures and by rising body temperatures (Grayson, 1949). The experimental subjects were mainly healthy men students, and a heating cabinet was used in which they sat with head and right arm outside; blood flows were measured by venous occlusion plethysmography in the fingers and forearm of the right arm. It was thus possible to correlate accurately peripheral blood flow with ambient temperature. Three phases were described in the responses of the finger circulation to rising cabinet temperatures.

(1) During the early stages of body heating, an increase occurred in the skin blood flow, most marked between cabinet temperatures of 28° and 36° C.; at the same time the rectal temperature fell or remained steady.

(2) As the cabinet temperature rose above 36° C. a significant drop in blood flow occurred.

(3) After prolonged exposure of the subject to temperatures of 40° C. or over, the rectal temperature rose, perspiration began, and the skin blood flow rose to a final equilibrium.

Further investigation made it clear that the low blood flows seen where the cabinet temperature was below 28° C. were the result of reflex vasoconstriction initiated at the body surface by exposure to an environment colder than the body. The vasodilatation seen in the first phase of the triphasic response was thus brought about by removing external stimulus of cold. The vasoconstriction seen in the second phase was shown to be a reflex response initiated at the body surface by exposure to temperatures hotter than that of the body. Reflex vasoconstriction to cold or heat could both be regarded as protective reactions in the presence of unfavourable environmental temperatures. The final vasodilatation following prolonged exposure to high temperatures always accompanied a rise in rectal temperature, and it was thought that this part of the response might well be brought about by circulating warmed blood. The efferent pathway for all these reactions was shown to be in the sympathetic nerves.

In the above investigation, 57 experiments were carried out on 53 subjects, none of them suffering from obvious circulatory disease; 48 subjects gave the reactions to heating just described. In the other 5 subjects and a further 5 cases of Raynaud's disease and acrocyanosis, curves of a different type were obtained. The investigation of these abnormal findings and a further elucidation of the factors underlying normal vasoconstrictor responses to cold and heat forms the basis of the present work.

METHODS

In the experiments just described, a thermostatically controlled heating cabinet was used in which the subject sat with his head and right arm protruding and exposed to the room air at 20° C. Blood flow changes in the fingers were recorded using a venous occlusion plethysmograph of a

type first suggested by Professor A. A. Harper, and described in detail elsewhere (Grayson, 1949). In most of the 57 experiments referred to, the plethysmograph was used in a water bath at 31° C. and sealed to the hand with the metacarpal heads enclosed. Under these conditions, with intensive body heating, the maximum recorded blood flows were usually about 15·5 ml./100 ml. of tissue/min. In 17 of the experiments, the same type of plethysmograph was used without the water bath and sealed to the hand at the base of the fingers by means of vaseline bandages. The maximum blood flows were now about 26·5 ml./100 ml. of tissue/min. The difference was shown to be largely due to the greater volume of non-expansible tissue within the plethysmograph when the metacarpal heads were included. The results with both types of recording were, however, qualitatively similar.

An additional 40 experiments have been recently performed in which the skin temperature of the right index finger was used as the index of the blood flow change. In these experiments, stimulus of cold was removed from the surface of the body by covering it with blankets. Skin and rectal temperatures were recorded thermoelectrically using moving-coil mirror galvanometers and a manually operated mechanical device to follow the movement of the light beam and give a continuous kymograph record of the temperature changes (Schmidt and Pierson, 1934). When all the body was covered, the temperature of the abdominal skin under the blankets rose rapidly and usually reached equilibrium levels of about 35° C. within 10 minutes. Thereafter, the cold and warmth vasoconstrictor responses were elicited by exposing different areas of the body surface to different temperatures.

Results

During heating experiments using the cabinet, the response of the finger circulation to changes in environmental temperature was usually rapid. A sudden rise in cabinet temperature anywhere in the range of 20° to 36° C. usually produced rapid vasodilatation, whereas a fall in cabinet temperature below 36° C. produced equally rapid vasoconstriction.

Delayed Vasodilatation During Heating Experiments

In five apparently healthy students, results were obtained that differed from those described. In experiments on these subjects, using the cabinet, no vasodilatation occurred in the skin (Fig. 1) during the first 90 minutes of heating when the ambient temperature rose from 20° C. to about 40° C. The hands remained cold, pale and dry, and the rectal temperature remained steady or fell. During the last 30 minutes, when the cabinet temperature was higher than 40° C. the rectal temperature rose. At the same time perspiration began and the blood flow in the fingers increased, the final blood flows reached being similar to those obtained in normal subjects (Table I).

TABLE I

Cold Hypersensitivity in non-Pathological Subjects

	Case No.	Cabinet Temperatures in °C. 20	25	30	35	40	45	50	Blood flows in ml./100 ml./min.
Air-filled	1	0·5	1·0	0·5	0 5	1·0	12·5	18·0	
	2	less than 0·5			1·0	1·0	10·6	—	
	3	2·3	2·2	2·6	2·9	3·2	12·9	27·9	
Water-filled	4	3·0	2·5	2·0	2·2	5·2	10·3	15·2	
	5	6·0	5·5	6·3	5·5	9·2	13·3	—	

Detailed questioning produced evidence in one case of numb and painful fingers in cold weather, and of frequent chilblains affecting the feet. In another where the hands were cold and cyanotic when exposed to the cold, chilblains affected alike the feet, hands and nose. One of the others

gave a doubtful history of chilblains in childhood. In the other two there was no history or clinical sign suggesting circulatory abnormality.

Delayed Vasodilatation in Raynaud's Disease and Acrocyanosis.—Four cases of Raynaud's disease and one of acrocyanosis were examined pre-operatively using the heating cabinet as described above. In all cases delayed vasodilatation of the kind already described was found, the blood flow in the fingers remaining low until after the rectal temperature had risen. The maximum blood flows finally recorded were normal.

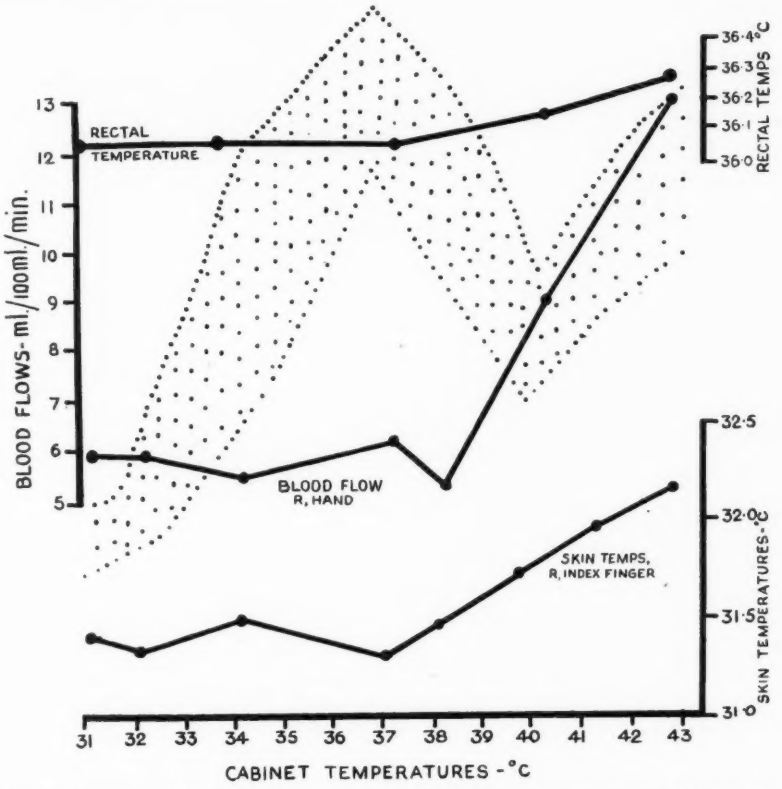

FIG. 1.—Delayed cutaneous vasodilatation in response to rising environmental temperature—"healthy" subject. The shaded area represents the limits of normal for blood flows in the series.

EXPERIMENTAL EVIDENCE OF COLD HYPERSENSITIVITY

It seemed possible that these abnormal findings, even where there was no clinical history to suggest it, might be the result of individual circulatory hypersensitivity to cold. This could be a local fault similar to that described in Raynaud's disease (Lewis, 1936), or might be more generalized. Additional experiments were consequently performed on certain of the subjects.

The Effect of Reducing Local Cold. Using the heating cabinet and plethysmographic recording of blood flow, a subject who had previously manifested typical delayed vasodilatation was exposed to rising environmental temperatures with the water in the plethysmograph at 31° C., and subsequently at 34° C. In both experiments the head and right arm were exposed to the room air at

20° C. and the blood flow remained at less than 4 ml./100 ml./min. until the cabinet temperature reached 41° C. Vasodilatation did not begin until after the rectal temperature had risen, the final blood flow reached on both occasions being 14·5 ml./100 ml./min.

Similar results were obtained with another subject examined with the water bath at 31° C. and again at 34° C. Thus, where delayed vasodilatation occurred in response to body heating, the results were not altered by local temperature.

The Effect of Reducing the Total Area of Body Exposed to Cold. The cabinet temperature was raised before the experiment to 35·0° C. (Fig. 2A). The subject sat inside and for 25 minutes finger blood flows were recorded from the right hand. More of his right arm was then enclosed within the cabinet and the blood flow observations repeated. Finally, the head and neck were totally enclosed for a period of about 10 minutes and the finger blood flow observations continued.

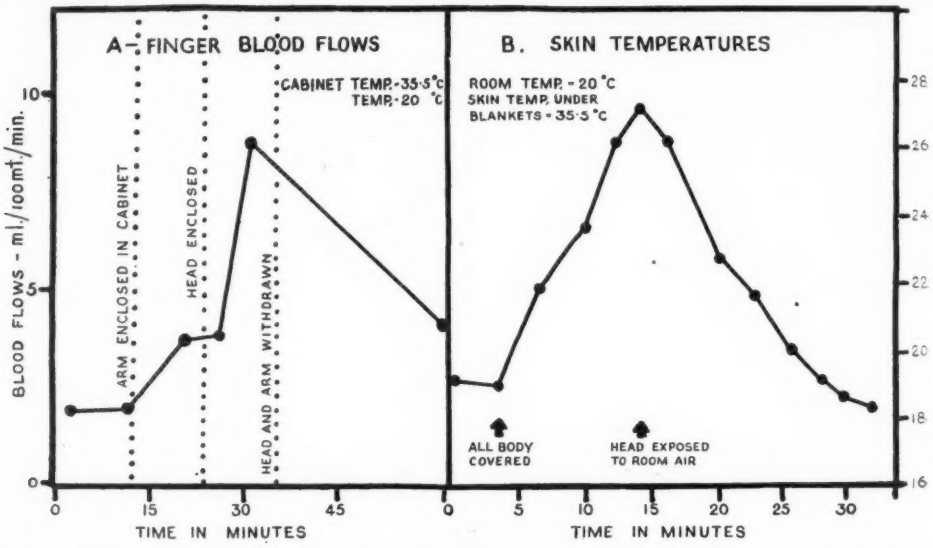

FIG. 2.—Cold hypersensitivity. The effect of exposing different areas of body to cold stimulus. (A) Blood flows. Subject seated in cabinet at 35·5° C. (B) Skin temperatures. Subject in room at 20° C. covered with blankets.

No rise in rectal temperature occurred, yet a considerable increase was recorded in finger blood flow.

On withdrawing the head and arm from the cabinet the finger blood flow fell again. It seemed, therefore, that the persistent vasoconstrictor tone was due to an abnormal sensitivity to cold—the exposure of the head, neck and arm to a temperature of 20° C. being sufficient to maintain a considerable degree of vasoconstriction.

The Role of the Sympathetic Nerves in Cold Hypersensitivity.—Sympathectomy was carried out in two cases of Raynaud's disease and one of acrocyanosis. Typical delayed dilatation in response to rising cabinet temperatures was recorded in all pre-operatively. The case of Raynaud's disease shown in Fig. 3 was investigated further before operation and shown to be " cold hypersensitive." Thus, with the cabinet at 36° C., enclosing all the body, including head and right arm, produced vasodilatation in the right hand. Vasoconstriction followed exposure of the face alone to the cold of the room. After preganglionic cervical sympathectomy the patient, examined daily during a period of three weeks, showed no evidence of " cold hypersensitivity," nor did intensive body heating produce vasodilatation. Similar results were obtained in all three cases.

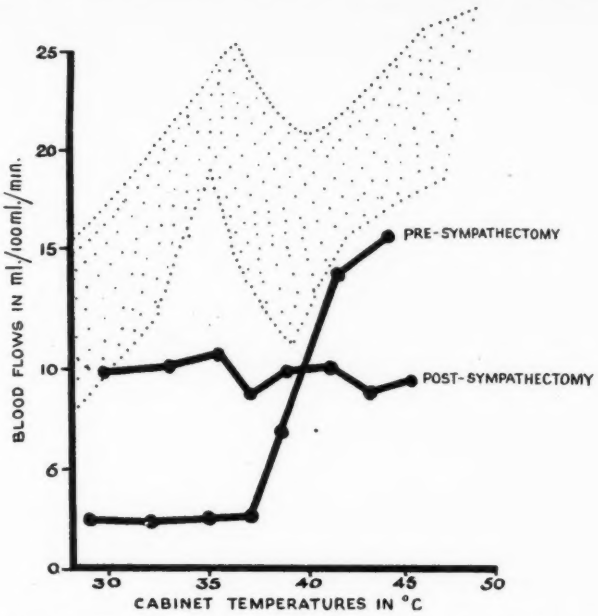

FIG. 3.—The effect of sympathectomy on delayed vasodilatation in a case of Raynaud's disease. Shaded area shows limits of normal for the series (air-filled plethysmograph).

"COLD HYPERSENSITIVITY" DEMONSTRATED BY THE SKIN TEMPERATURE METHOD

In 40 experiments already referred to, "cold stimulus" was removed from the surface of the body by covering with blankets. In most subjects, when all the body, including the head and neck, was covered, the skin temperature of the index finger (which alone remained exposed to the room) rose to about 35° C. with no change in rectal temperature (Table II). Exposing different parts of the body's surface to temperatures below or above body temperature caused cutaneous vasoconstriction (Fig. 4 and 5). Exposing the head and right arm to the room air at 20° C. thus usually

TABLE II

NORMAL SUBJECTS—SKIN TEMPERATURE CHANGES ON REMOVING "COLD STIMULUS"

	Skin Temperatures °C.		
Rectal temperature °C.	Body completely covered	Head and Neck exposed to room at 29° C.	All body exposed to room at 20° C.
37·2	—	32·0	23·1
37·2	36·1	33·5	27·0
36·9	35·2	32·2	19·0
37·1	34·9	32·5	19·0
37·1	—	33·0	22·0
37·1	—	31·0	23·4
37·0	—	32 4	31·2
37·1	—	34·0	29·6
37·0	35·0	33·0	25·0
37·1	34·8	33·1	25·4

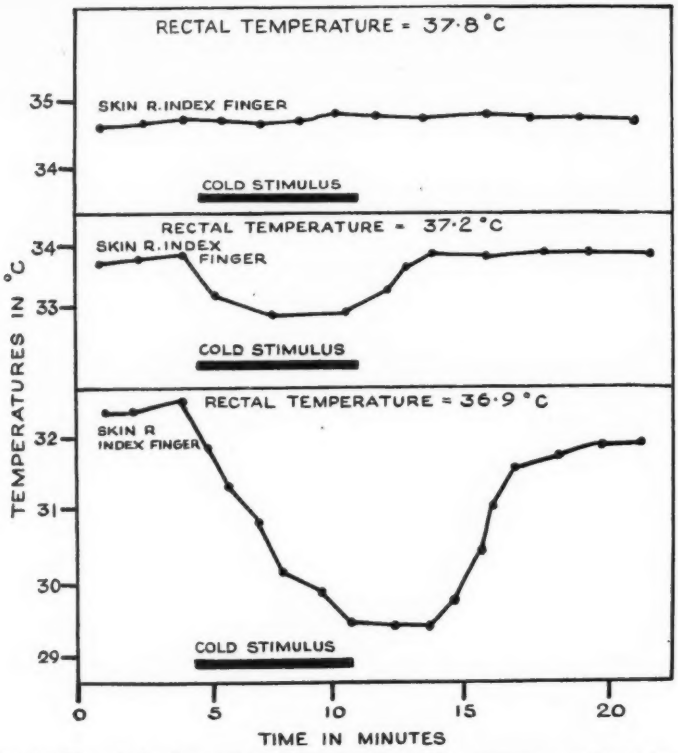

FIG. 4.—The relation between body temperature and the response to cold stimulus. Skin temperature observations in the normal subject.

produced a fall in skin temperature of about 2° C. In most subjects, therefore, covering all the body except the head and right arm raised the skin temperature of the index finger to maximum levels of 31° to 33·5° C.

In four subjects, however, the same procedure failed to produce vasodilatation in the right index finger (Table III), even where the skin temperature of the abdomen under the blankets rose to 35·4° C. However, with the head and right arm also covered, vasodilatation was produced. In the case shown in Fig. 2B the resting skin temperature was 19·4° C. rising on completely removing cold stimulus to 27·5° C., falling again on exposing the head alone to the cold of the room (19° C.). Subsequent exposure of the whole body had no greater effect and it must be assumed that the vasoconstriction produced by exposure of the face alone was practically complete.

Each of the four subjects, investigated on a number of different occasions, gave similar results. In one, examined 7 times in a period of 4 months, the same findings were always obtained and the evidence indicates the presence of "cold hypersensitivity" similar to that previously shown in plethysmographic records with a heating cabinet.

In two of the cases there was a history of chilblains in childhood, otherwise there was no suggestion of abnormal sensitivity to cold. On examination, however, each of the cases showed a slight, diffuse or mottled purplish coloration in the skin of the hands, particularly on the dorsum. Expelling the blood from the skin by firm stroking was followed by a slow, sluggish return of colour. Otherwise no abnormalities were found.

TABLE III

COLD HYPERSENSITIVE SUBJECTS—SKIN TEMPERATURE CHANGES ON REMOVING "COLD STIMULUS"

Rectal temperature °C.	Skin Temperature °C.		
	Body completely covered	Head and neck exposed to room at 20° C.	All body exposed to room at 20° C.
36·1	32·5	22·8	22·8
36·1	30·5	19·4	19·3
36·5	31·0	20·2	20·2
36·1	28·5	21·4	21·6
36·0	27·4	19·5	19·8
36·3	26·8	21·2	21·0

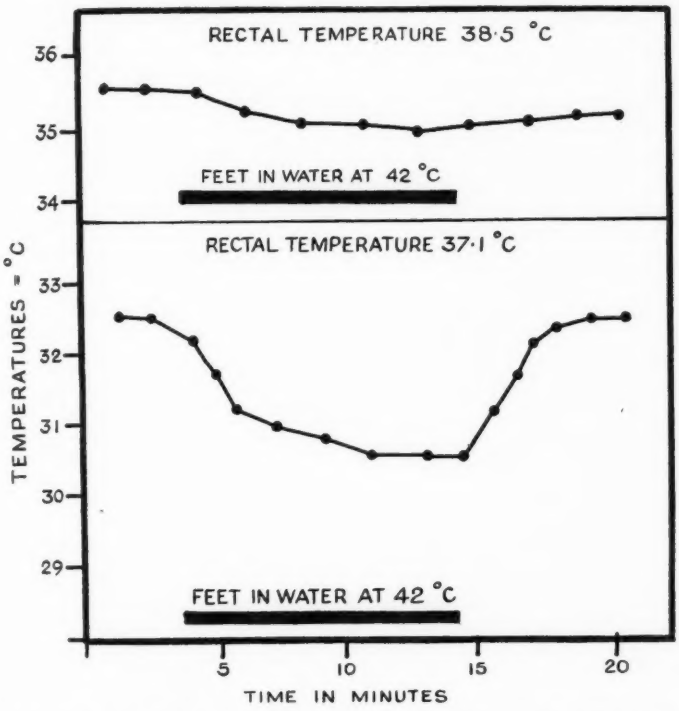

FIG. 5.—The effect of raising the body temperature on the response to heat stimulus. Skin temperature observations in the normal subject.

THE EFFECT OF "BODY TEMPERATURE" ON THE WARMTH AND COLD CONSTRICTOR RESPONSES

In order to throw additional light on the nature of the abnormalities described, the relation between "body temperature" and the sensitivity of the cold and warmth response was investigated in normal and "cold hypersensitive" subjects. Rectal and mouth temperatures were both measured thermoelectrically. The latter were unreliable, and the former were subject to slight variations related to the intestinal circulation (Grayson, 1950). However, as a record of relatively

gross changes in internal temperature rectal records were regarded as the most satisfactory method available at the time.

The effect of rising environmental temperatures on the sensitivity of the cold and warmth vasoconstrictor reponses in normal subjects. Using the heating cabinet in the investigation of the normal subject, it was found that once the rectal temperature had risen, lowering the cabinet temperature produced no vasoconstriction in the hand until the rectal temperature itself returned to " normal " (Grayson, 1949).

This phenomenon was investigated further by the skin temperature method. In 6 experiments the body temperature of normal subjects was raised by covering the body with blankets and immersing the legs in hot water, and cold or warmth vasoconstrictor responses recorded at different rectal temperatures. In the case shown in Fig. 4 each observation was made with the body covered with blankets, except for the head and right arm. The cold constrictor stimulus used was the exposure of the anterior abdominal wall to the cold air of the room. Raising the rectal temperature from 36·9° to 37·2° C. produced a rise in skin temperature from 32·5° to 33·7° C. The intensity of the vasoconstrictor response was greatly diminished. When the rectal temperature had risen to 37·8° C. the skin temperature rose to a fresh equilibrium level of 34·8° C. The cold vasoconstrictor response was now entirely abolished.

The effect of heat stimulation was also investigated. In the experiment shown in Fig. 5 the subject was covered with blankets except for the head and right arm; the legs were immersed in water at 36° C. during the resting periods. Heat stimulation was produced by transferring the legs to a water bath thermostatically maintained at 42° C. and stirred continuously. Again, the heat constrictor response was reduced in intensity by small increases in rectal temperature, and abolished in the presence of high rectal temperatures.

Similar results were obtained in all cases. Although the methods used were not strictly quantitative, it is clear that in normal subjects raising the rectal temperature inhibited the cold and warmth vasoconstrictor responses.

Rising Body Temperature in Cold Hypersensitive Subjects. The effect of body temperature variations was studied in four cold hypersensitive subjects (Table III). In these, the average of 6 resting rectal temperatures measured on different days was 36·2° C. In a group of 10 normal subjects the average resting rectal temperature measured under the same conditions was 37·1° C. (Table II). Statistical examination shows a significant difference between the two groups ($t=12{\cdot}500$; $P=0{\cdot}001$) the rectal temperatures of the cold hypersensitive subjects being lower than those of the normal subjects.

Experiments were performed in which the effect of raising the rectal temperature of the subjects was investigated. A cold hypersensitive subject was covered with blankets except for the head and right arm (Fig. 6). At the beginning of the experiment the rectal temperature was 36·5° C. and the resting skin temperature remained at 23·6° C. despite a rise in temperature under the blankets of 35·2° C. The rectal temperature was raised to 36·9° C. by immersing the legs in hot water at 45° C., when the skin temperature of the index finger rose to 32·5° C. Exposure of the abdominal wall to the room air now produced a normal cold constrictor response. The rectal temperature was raised still further to 37·4° C., the skin temperature now rose to 34° C. Exposure of the abdominal wall now had no vasoconstrictor effect.

The experiment was repeated on another subject with similar results. Thus in cold hypersensitive subjects, when the rectal temperature was within the range of normality the cold vasoconstrictor effect was normal. When it was still higher, the cold vasoconstrictor response of the cold hypersensitive subjects was completely inhibited.

Discussion

Previous investigations have shown that rising environmental temperatures can produce rapid vasodilatation in the skin even when the rectal temperature is falling (Cooper and Kerslake, 1949;

Grayson, 1949). Under the experimental conditions of the present investigation, however, a well-defined group of subjects has been found who do not respond quickly to changes in environmental temperature, but only produce full vasodilatation after the body temperature has risen. This group included several subjects with no clinical signs of circulatory abnormality and some who, whilst not requiring clinical treatment, showed signs of exaggerated circulatory sensitivity to cold; it also included several with frank pathological involvement of the peripheral circulation.

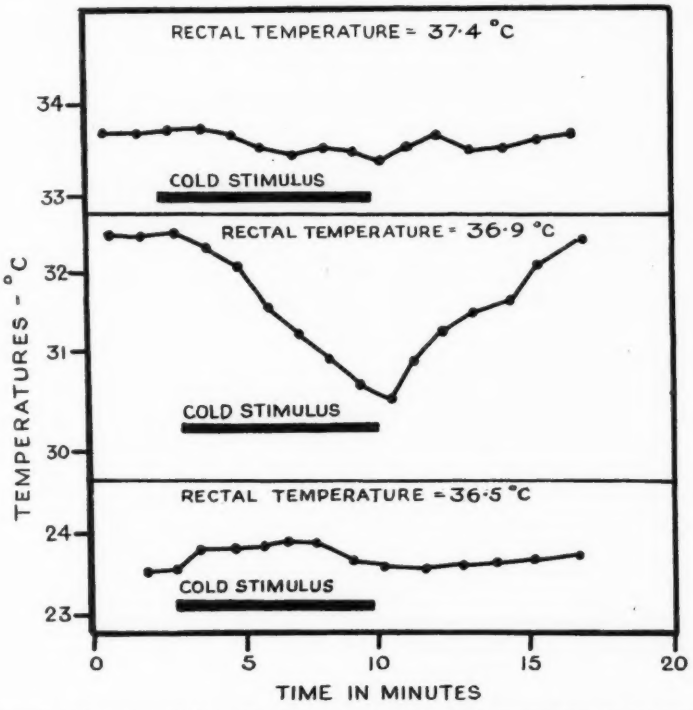

FIG. 6.—Cold hypersensitivity. The effect of raising the body temperature on the response to cold stimulus. Skin temperature records in cold hypersensitive subject.

The evidence available indicates that these abnormal findings depend on the experimental conditions. Thus they were only obtained when the head and neck and upper arm of the subjects were exposed to the cold of the room. When the whole of the subject was enclosed in the cabinet or covered with blankets, the abnormal constrictor tone was abolished. On the other hand, where the plethysmograph was used, the local temperature of the hand appeared to have little effect on the result. It may be concluded, therefore, that there is present in these subjects a state of cold hypersensitivity in which exposure of the head, neck and upper arm to temperatures of 20° C.—the room temperature—is sufficient to maintain a considerable degree of vasoconstrictor tone, even when the rest of the body is exposed to temperatures as high as 40° C.

Experiments before and after preganglionic cervical sympathectomy indicate, moreover, that this cold hypersensitivity depends on the integrity of the sympathetic innervation of the vessels. It would seem that there is some overactivity of the cold constrictor reflex.

The standards of cold hypersensitivity investigated in this way are purely arbitrary. It might be expected that if more of the body were exposed to cold as a routine, a higher percentage of cold

hypersensitive subjects would be found. Indeed, when subjects were heated in a cabinet leaving the extremities and head and neck exposed to the room, Lewis and Pickering (1931) showed that vasodilatation never occurred until after the rectal temperature had risen. It could be argued that, under these conditions, sufficient of the body surface is exposed to the relative cold of the room to maintain a high degree of vasomotor tone even in normal subjects.

The phenomenon of " cold hypersensitivity " cannot be understood further without considering the relation between body temperature and normal cold and warmth vasoconstrictor responses. Body temperature in itself has a profound effect on the skin circulation (Pickering, 1932). Thus, raising the body temperature produced vasodilatation, lowering the body temperature vasoconstriction, irrespective of external cold or heat stimulus. But it is also clear that body temperature equally affects the sensitivity of the cold and warmth vasoconstrictor responses. Thus these effects are diminished in intensity or even totally inhibited in the presence of high rectal temperatures.

These experiments suggest that " cold hypersensitivity " in subjects at rest may also be a function of body temperature: it may be significant that the rectal temperature is significantly lower in them than in normal subjects. Moreover, " cold hypersensitivity " can be abolished by raising the rectal temperature, and it is clear that the reflex mechanism underlying cold vasoconstriction is just as subservient to general body temperature in cold hypersensitive as in normal subjects.

It is premature to speculate on the possible role of " cold hypersensitivity " as a predisposing factor in peripheral vascular disease, but it is worthy of note that the five vasopastic cases examined all manifested this abnormality.

Summary

Venous occlusion plethysmography and skin temperature measurements were used to detect skin blood flow changes in human subjects.

Stimulus of cold was removed from the surface of the body either by means of a heating cabinet warmed to 36° C. or by covering the subject with blankets.

Removing cold stimulus produced considerable skin vasodilatation in normal subjects without significant change in rectal temperature.

Subsequent exposure to temperatures hotter or colder than the body causes reflex vasoconstriction in the skin. The response is diminished or abolished by high rectal temperatures.

In some apparently healthy men, the cold vasoconstrictor responses are exaggerated under the usual resting conditions. The resting rectal temperature of subjects in this group is significantly lower than that of normal subjects. Moreover, raising the rectal temperature abolished " cold hypersensitivity." " Cold hypersensitivity " has been found in a few cases of Raynaud's disease and acrocyanosis.

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NUTRITIONAL HEART DISEASE

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The prevailing concept of beri-beri heart disease is based on the syndrome described by Alsmeer and Wenckebach (Wenckebach, 1928, 1932, 1934; Alsmeer and Wenckebach, 1929). It was heart failure characterized by sinus rhythm, systemic venous engorgement, peripheral œdema, and signs of a fast circulation such as bounding pulses and pistol-shot sounds over the major arteries. They emphasized that the failure was exclusively of the right heart. The electrocardiogram was normal except for a "certain degree of preponderance of the right ventricle." Enlargement of the heart was progressive, but whereas in the earliest phase of the disease this involved the whole heart, subsequent enlargement chiefly affected the right side. Histologically, the salient lesion was "hydropic" degeneration of the myocardium. Wenckebach attributed the whole syndrome to water retention. He regarded the functional defect of the myocardium as one of contractility, conduction being unimpaired. The disease was endemic in the Dutch East Indies.

Weiss and Wilkins (1936, 1937) reported a high incidence of "beri-beri heart" among chronic alcoholics in America. The disease that they described, however, differed considerably from oriental beri-beri. Some of their patients did have a hyperkinetic circulation and dominant failure of the right heart but still more "with an identical type of deficiency showed pulmonary engorgement with dyspnœa, cardiac asthma, orthopnœa, and other manifestations of left-sided failure." They remarked that although vitamin B_1 deficiency was principally the cause of alcoholic beri-beri as of the oriental variety, the response to treatment with the vitamin was not uniform. The most striking thing about the subsequent reports on the cardiac form of beri-beri is the variability of the disease that is described under this name. Only rarely does it conform to the criteria of Alsmeer and Wenckebach and recently the trend has been to deny any specificity to the syndrome (Dock, 1940; Hussey and Katz, 1942; Vilter, 1945. Blankenhorn, 1945). Failure to respond to aneurin in adequate dosage is not regarded as compromising the diagnosis (Hussey and Katz, 1942; Blankenhorn, 1945).

The purpose of this paper is to describe a form of heart disease that is thought to be caused by malnutrition. It is not the same disease as that described by Alsmeer and Wenckebach. It is unaffected by aneurin and will not, for these reasons, be referred to as beri-beri. It has the further characteristic of being invariably associated with progressive liver disease of a kind that is known to be caused by malnutrition (Gillman and Gillman, 1945).

Clinical Material

The following account is based on 30 Bantu patients with heart failure of this kind who have been observed during the past eighteen months. Of the thirty, 22 were men and 8 women; the youngest was aged 30 and the oldest 63 years. It is necessary to emphasize that these figures have no significance other than that the disease is not a rare one in the urban Bantu community from which these patients were drawn. Certainly the disease occurs in childhood.

Dietetic History

The diet of all patients consisted of porridge made from highly refined maize, supplemented with white bread, tea, and sugar. Meat and milk were consumed in very small quantity or not at all, and only rarely were vegetables or fruit added. This, indeed, is the staple diet of the Bantu community in urban areas (Phillips, 1938; Fox, 1941). The scale of nutrition is set by low wages which, under ideal domestic budgeting, are not sufficient to provide the nutritional requirements for a minimum standard of health (Blair, 1947). Added to this, perhaps not unnaturally, is ignorance of the nutritive value of the various foods that are for sale in the towns.

Clinical Features

The ultimate disablement of most patients is caused by dropsical swelling of the whole body. It begins in the feet and spreads upwards to involve the trunk, upper limbs, and face. Twenty-six patients described their dominant symptom in this way. All had dyspnœa on effort but only three referred to this symptom before all others; none had had paroxysmal nocturnal dyspnœa or effort pain. One patient sought medical advice primarily on account of neuritic symptoms although he had heart failure at the same time. Additionally, twelve patients complained of a dry cough and sixteen of pain in the right upper quadrant of the abdomen. Of the eight women three were past the menopause, four had amenorrhœa, and one menstruated regularly.

Duration of symptoms. The South African Bantu has a singularly negative attitude to time and for that reason (and others) it is difficult to discover the precise duration of the symptoms complained of. Among those who were in hospital for the first time the reputedly longest duration of symptoms was four weeks, the shortest three days. It may be said with reasonable certainty that in contrast to the extreme *signs* of disease the duration of *symptoms* is surprisingly brief. Nineteen had previously been in hospital on account of heart failure, eight on more than one occasion and one as often as eight times. Of these the longest period between successive admissions was four months, the shortest two weeks.

Signs. The most striking feature of all patients with a single exception was œdema of extreme degree. In distribution it was generalized, although maximum in the lower parts of the body. The neck veins were engorged and the brachial venous pressure high (Table II). Chemosis was obvious in most patients; three had subconjunctival hæmorrhages. Six had proptosis, interpreted as due to venous engorgement within the orbit, but none had either papillœdema or retinal hæmorrhages. Twenty-seven of the thirty patients had clinically recognizable ascites; in twenty-three of these the abdomen was tensely distended. Thirteen had hydrarthrosis of both knees and six had bilateral hydrocele. In contrast, only seven patients had hydrothorax. This was bilateral in three instances; in the remainder the right and left sides were equally involved. The estimated protein content of œdema fluid from various sources is shown in Table I. The liver was invariably enlarged and, initially, tender. Crepitations were heard over the basal parts of the lungs in twenty-five patients.

TABLE I

Percentage Protein Content of Œdema Fluid

	Subcutaneous	Ascitic	Pleural	Hydrocele	Joint
Range	0·05–0·60	2·0–6·0	1·2–4·0	2·4–5·0	2·0–3·2
Mean	0·2	3·6	2·8	3·9	2·7
Number of patients ..	10	6	6	5	4

Almost all patients when admitted to hospital preferred to sit up supported, rather than to lie recumbent. Two patients adopted the knee-elbow position by choice; they slept in this position. In darkly pigmented people the presence or absence of cyanosis is too difficult to assess to be a reliable sign. The hands of most were regarded as being cold; strikingly warm hands were never

observed notwithstanding that six patients had mild fever during the first few days that they were in hospital. Arterial pulses were of small volume, never bounding; pistol-shot sounds were not heard in these patients.

TABLE II

HEART RATE, VENOUS PRESSURE, AND CIRCULATION TIMES PRIOR TO ANY FORM OF TREATMENT

	Heart rate per minute	Brachial venous pressure, mm. saline above sternal angle *	Arm to tongue time, seconds	Arm to lung time, seconds	Lung to tongue time, seconds
Range	72–120	85–350	15·0–84·0	6·0–46·0	5·0–47·0
Mean	94	220	39·8	22·7	15·7
Standard deviation ..	12·8	87·1	19·2	11·1	9·1
Number of patients	30	19	27	24	24

* Patient supported in position of 45-degrees recumbency.

The heart was enlarged in all. Its size and shape will be referred to in detail below. The cardiac impulse was feeble or, more commonly, impalpable. Heart rates at the time of admission to hospital ranged from 72 to 120 (Table II). Sinus rhythm was invariable. All had a diastolic gallop. In twelve instances the gallop was thought to be presystolic in type and in six protodiastolic; in the remainder the rate was too fast for the extra heart sound to be timed more accurately by auscultation alone. Two patients had infrequent ventricular extrasystoles. Sixteen had a systolic murmur, heard maximally at the apex. The highest systolic pressure recorded at the time of admission to hospital was 152, the lowest 90. Corresponding maximum and minimum diastolic pressures were 90 and 70. Pulse pressures varied from 16 to 62 (Table III). In two patients pulsus alternans was perceptible at the wrist; in ten others there was alternation in the upper 10 to 15 mm. of the systolic pressure scale. This sign was not constantly recorded; if it had been it is probable that its frequency would have been higher. Mean circulation times were prolonged over arm to lung and lung to tongue segments (Table II). In individual patients lung to tongue time was a reasonable measure of pulmonary congestion.

TABLE III

BLOOD PRESSURE DURING PERIOD IN HOSPITAL

	On admission			Maximum recorded in course of clinical improvement		On discharge	
	Systolic	Diastolic	Pulse Pressure	Systolic	Diastolic	Systolic	Diastolic
Range	90–152	70–90	16–62	105–156	80–108	104–140	70–90
Mean	122	83	39	133	95	119	79
Standard deviation	17·8	7·7	14·5	14·8	6·2	11·2	5·0
Number of patients	30	30	30	21	21	21	21

Most patients had some albumen in the urine but no significant microscopic content. Glycosuria was excluded by routine examination. The test for ketone bodies was not always done (because its significance was not originally realized) but certainly some patients had ketonuria. The eye grounds of all were normal apart from engorgement of veins. None had primary lung disease by clinical and radiological standards. Ova of *Ascaris lumbricoides* were found in the fæces

of six patients. There was no evidence of chronic malaria, bilharziasis, or other parasitic infection in any. Twenty-one patients had signs of peripheral neuritis. One of these had quadriparesis. The remainder had little apparent loss of motor power but in all the knee or ankle jerks, or both, were absent. It was estimated that ten of these had depressed sensation in the distal parts of the lower limbs.

Seven patients had a pellagrous dermatosis. None complained of a sore tongue and none had stomatitis or diarrhœa. In three patients there was a minor abnormality of the tongue; it was a little reddened and raw at its margins but in no instance closely resembled the kind that has been attributed to deficiency of various components of the vitamin B complex. In the African, testicular atrophy, gynæcomastia, and parotid gland enlargement are reputed to be consequences of malnutrition (Davies, 1948, 1949). It is difficult to recognize minor degrees of testicular atrophy but this sign was recorded in fourteen patients. Sixteen had gynæcomastia. Paratosis was observed in one instance only.

Laboratory Investigations

The results of these investigations are shown in Tables IV and V. Quantitative tests of this kind and, indeed, all quantitative tests must be interpreted with caution for there is little knowledge

TABLE IV

Alteration of Plasma Protein Percentage During Treatment

	On admission			On discharge		
	Total protein, g. per cent.	Albumen, g. per cent.	Globulin, g. per cent.	Total protein, g. per cent.	Albumen, g. per cent.	Globulin, g. per cent.
Range	4·5–8·5	2·4–5·2	1·4–4·2	5·4–9·7	3·0–4·9	2·1–5·4
Mean	6·1	3·4	2·7	7·1	4·0	3·1
Standard deviation	1·0	0·7	0·6	1·2	0·5	0·9
Number of patients	30	30	30	20	20	20

of physiological values in the Bantu. Relative to normal values in other communities (Moore and Van Slyke, 1930; Trevorrow, *et. al.*, 1941) plasma albumen levels are low and globulin levels high. In the individual patient, however, plasma albumen concentration did not correlate with the amount of œdema, nor with the severity of the disease by any other clinical standard. The increase in plasma globulin did appear to bear a direct relation to the degree of liver injury as estimated by biopsy or post-mortem examination.

Serum sodium and potassium do not differ from reported normal values (Harrison, 1947; Cecil, 1947). The mean plasma cholesterol level is low although a wide scatter is revealed. More significant perhaps is the range of fasting blood sugar which is almost certainly on a lower scale

TABLE V

Biochemical Investigations of Blood and Serum

	Serum potassium, mg. per cent.	Serum sodium, mg. per cent.	Plasma cholesterol, mg. per cent.	Blood urea, mg. per cent.	Fasting venous blood sugar, mg. per cent.	Hb., g. per cent.
Range	16–24	308–362	80–260	16–60	60–97	12·9–19·5
Mean	19·6	333·6	113·6	34·4	77·5	16·0
Standard deviation	1·5	14·0	41·6	11·7	12·0	1·6
Number of patients	22	23	23	23	21	22

than the normal in the same race. The mean hæmoglobin value in healthy European adult men at the altitude of this city is 17·8 grams., in women 15·3 grams per 100 ml. (Lurie, 1949). The mean for both sexes is not significantly different from that in the patients now under consideration. Where blood urea was raised this was a pre-renal effect. Among those who survived there was no recognizable impairment of renal function after recovery from heart failure, and of those that died none had renal disease.

Radiological Examination

The heart was enlarged in all, in most instances grossly so. Invariably the enlargement affected both sides of the heart. In proportion to the degree of enlargement the heart became globular in outline. The middle arc of the left cardiac border was inconspicuous. The appearance of the aortic arch was not abnormal. The amplitude of cardiac (and aortic) pulsation was minimal and this applied irrespective of the degree of enlargement and of rate in the untreated patient. Congestive changes in the lung fields or engorgement of the pulmonary veins were observed in twenty-seven patients; in the remainder the lung fields were strikingly clear (Fig. 9). As already mentioned, three had bilateral, and four unilateral hydrothorax.

The enlarged, globular, inert heart is fluoroscopically characteristic, although not necessarily pathognomonic. It resembles the type of heart that is attributed to myxœdema, a diagnosis that was rigidly excluded by other standards. Nevertheless, the differential diagnosis from pericardial effusion was at times questioned, and in twelve patients the pericardium was needled on one or more occasions but never was it possible to aspirate fluid. This corresponded to post-mortem findings. Illustrative teleradiograms are shown in Fig. 1, 2, 4, 5, 7, 8 and 9.

The Electrocardiogram

Twenty patients were examined by standard and unipolar leads. Of these, by cardiographic standards (Bain and Redfern, 1948), eleven had left ventricular hypertrophy with a horizontal or semi-horizontal position of the heart; three had the pattern of left ventricular hypertrophy in præcordial leads but with a vertical heart in each instance, presumably implying hypertrophy of both ventricles. One had right ventricular hypertrophy with a vertical axis and two had right bundle branch block. In the remaining three neither ventricle was cardiographically dominant. These patterns were preserved throughout the course of the illness and did not alter with recovery. The most constant feature of the electrocardiogram was a curve of subepicardial injury and this was observed in twelve patients (Fig. 3 and 6). In these the electrocardiogram did not usually become stabilized in less than ten weeks. The P–R interval was prolonged beyond 0·2 second in one patient; he also had right bundle branch block. Of the twenty patients ten had low voltage QRS complexes in unipolar limb leads (Goldberger, 1947).

Ten patients were examined by standard limb leads and two or more bipolar chest leads. For technical reasons some of these records were unsatisfactory and in most instances only a single cardiogram was available. Of the ten, five had low voltage QRS complexes, four had left axis deviation, and two right axis deviation. T1 or T1 and T2 were inverted or isoelectric in seven patients. The P–R interval was prolonged in none. All had sinus rhythm; two had ventricular extrasystoles.

Ætiological Diagnosis

It was obvious from the time when this disease was first encountered that it did not conform to any of the common categories of congestive heart failure. The preliminary stages of establishing an ætiological diagnosis preceded the planned investigation that forms the basis of this paper. Clinically the dynamic quality of the circulation indicated that the cardiac output was low. It was argued for that reason that digitalis would not be harmful. It transpired that it was not helpful—at least not in these early cases that were admittedly severe.

Notwithstanding the dissimilarity from beri-beri heart failure the known inadequacy of the patients' diet (including deficiency of vitamin B_1) made consideration of this diagnosis imperative. Accordingly treatment with intravenous thiamin in dosage varying from 50 to 150 mg. daily was tried. At the same time the patients were confined to bed in hospital and given a well-balanced diet. No attempt was made to restrict the intake of sodium chloride. None of the dramatic recoveries reported in beri-beri occurred, but over a period of 7 to 10 days some patients improved greatly. In these, after two to three weeks, œdema had disappeared and heart size had become much smaller. It was then decided to try the effect of the same diet without added thiamin. Precisely the same favourable result occurred in the same proportion of patients and in as short a time. It was at this stage that the present investigation began.

Five patients in moderately severe failure, on being admitted to hospital, were confined to bed and given a diet similar, so far as was possible from the information they gave, to their accustomed diet at home. This consisted of porridge made from refined maize, half a pint of milk daily, tea, sugar, white bread, and jam. The quantity of milk only was controlled. Without exception their clinical condition deteriorated; they gained weight and œdema became more pronounced; heart size increased further (Fig. 1). There is obviously a limit to which this type of observation can be pursued but it is justified because present circumstances make it inevitable that these patients will revert to the same diet as soon as they leave hospital. After not more than two weeks on this restricted diet the patients were given the standard diet already referred to. In one to three weeks time œdema disappeared and distension of neck veins ceased to be apparent in all. In two of the five heart size returned to normal (Fig. 1); in the remainder it diminished considerably but failed to revert to normal. This residual enlargement, which will be discussed below, did not yield to any subsequent treatment. The remaining 25 patients were placed on an optimum diet from the time of their admission to hospital. Seven of these made a complete recovery in so far as all œdema disappeared, venous pressure fell to normal (as judged by the absence of distension of cervical veins) and enlargement of the heart was no longer apparent (Fig. 2 and 4). This favourable result occurred in less than four weeks in all, and with no other treatment than wholesome food. At that stage six of these patients, while still confined to bed, had their diet restricted as in the previous group but supplemented as follows: two were given 25 mg. of aneurin, two were given 10 grams of brewers' yeast, and two were given 500 mg. of alpha-tocopherol acetate each day (the rationale of this and other therapeutic trials will be discussed subsequently). The longest period over which this controlled diet was continued in any instance was three weeks. An enlarging heart, an increase in peripheral venous pressure, and a recurrence of œdema was apparent in all (Fig. 2, 4 and 5). These changes were reversed when the original diet was resumed. The basic pattern of the electrocardiogram was not noticeably influenced by restriction of diet over this brief period.

It follows from what has been stated that nine patients made an apparently complete recovery from heart failure on dietetic treatment alone (their recovery was not complete in other respects). Thirteen patients made a partial recovery on the same treatment. In these, when maximum improvement had been obtained by this means, dietetic treatment was supplemented in one or more of the following ways:

(*a*) Thirteen patients were given 2 ml. of mersalyl intramuscularly every other day or twice weekly for periods ranging from 3 weeks to 3 months. In eight of these the drug caused an increased urinary excretion and weight loss varying from 1·3 to 4·5 kg., but further benefit was not forthcoming and in no instance was the œdema dispelled. No perceptible effect on heart size or circulatory efficiency was observed in any.

(*b*) Ten patients were given digitalis. No sustained improvement in the circulation followed. There was no change in heart size nor was there significant weight loss in any patient.

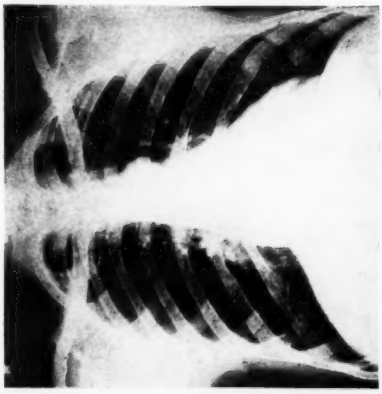
(*c*) The combination of digitalis and mersalyl was tried in eight patients. The effect was not apparently better than that due to mersalyl alone.

(*d*) Ten patients were given 50 to 200 mg. of aneurin daily for periods varying from 10 to 20 days. No beneficial effect was observed.

A

B

C



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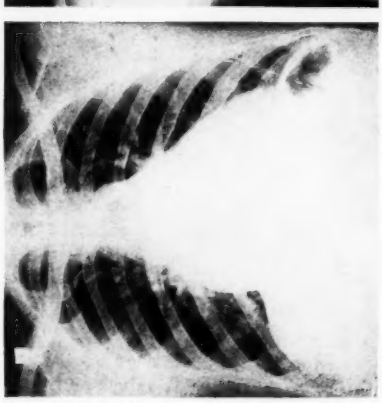
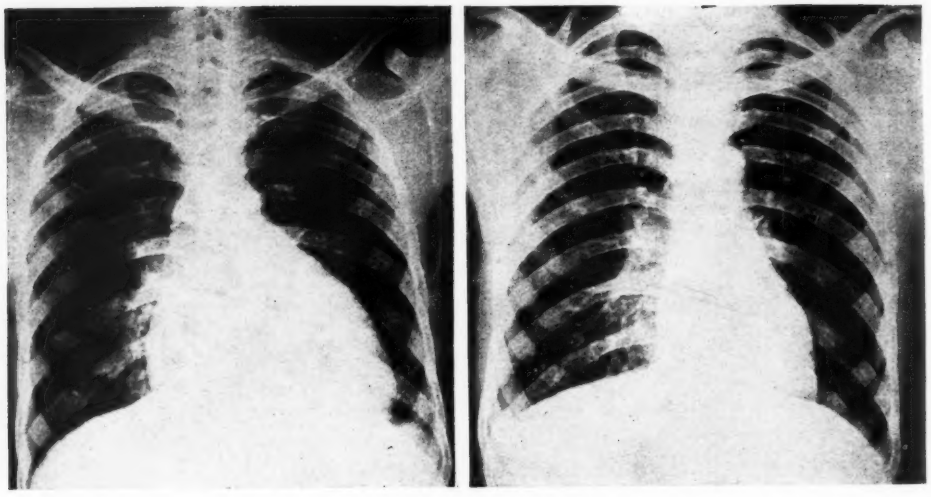


E

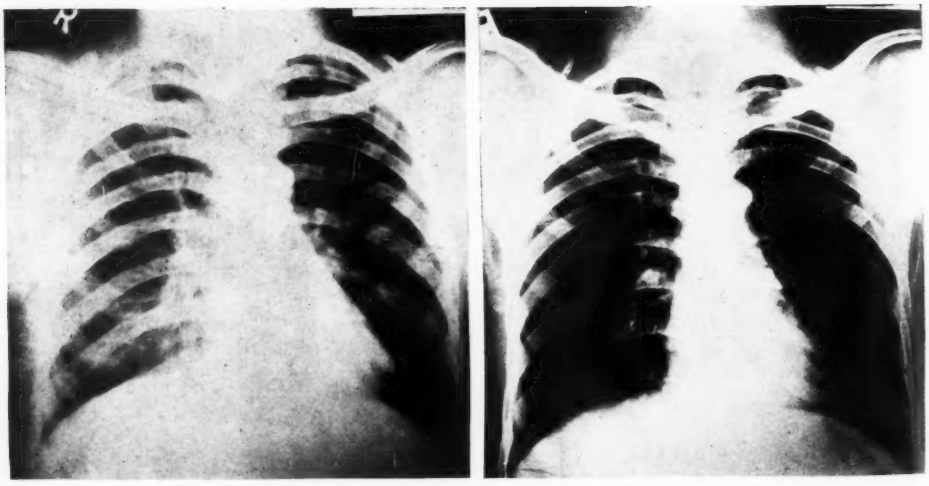
(A) As on admission, 18/11/48. Enlargement of all chambers of heart. Congestive failure.
(B) 25/11/48. On restricted diet, supplemented with 500 mg. alpha-tocopherol daily, since admission. During this time gained 15 pounds in weight. Increasing venous engorgement and œdema. Further increase in heart size.
(C) 9/12/48. On standard hospital diet since 25/11/48. Diminution in heart size. Weight loss 40 pounds. Minimal engorgement of neck veins persisting but no apparent œdema. Patient insisted on being discharged at this stage. Seen again 5/1/49 when heart size was greater and signs of congestive failure more advanced.
(D) 3/8/49. Re-admission to hospital with gross right heart failure.
(E) 15/8/49. Recovery from heart failure with no treatment other than standard diet. Heart size now normal.

FIG. 1.*—Man, aged 34 (Reference No. 16434/48).

* These and subsequent reproductions are of 6-ft. teleradiograms.



A B



C D

FIG. 2.—Man, aged 30 (Reference No. A12681).

(A) As on admission, 5/4/49. Enlargement of all chambers of heart. Congestive failure.
(B) 3/5/49. Patient has received no treatment other than standard hospital diet. Heart size now normal. Systemic veins no longer engorged. No œdema. Weight loss 52 pounds.
(C) 12/5/49. On restricted diet, supplemented with 25 mg. aneurin daily, since 3/5/49. Teleradiogram shows increase in heart size. Neck veins again distended; œdema over sacrum.
(D) 26/5/49. Resumed standard diet on 12/5/49. Heart size normal. Recovery from congestive failure. No supplementary treatment of any kind.

Corresponding electrocardiograms are shown in Fig. 3.

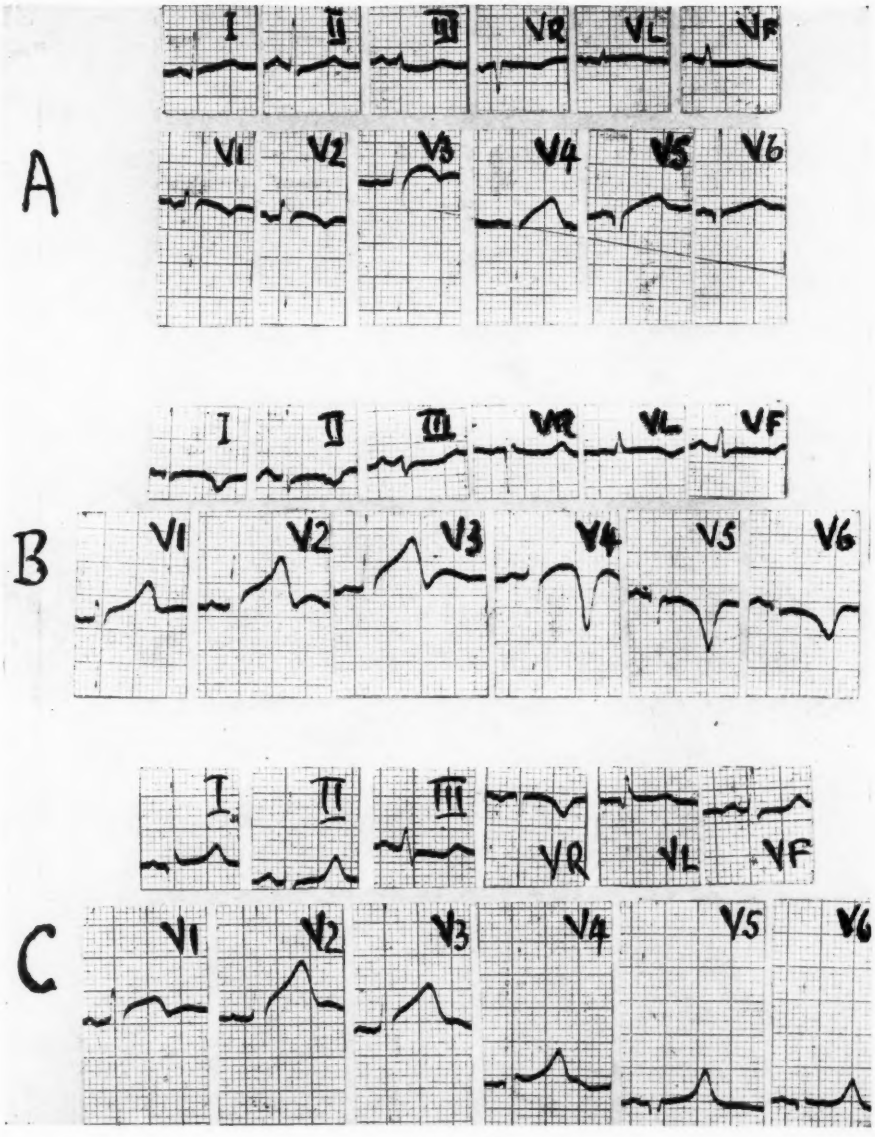
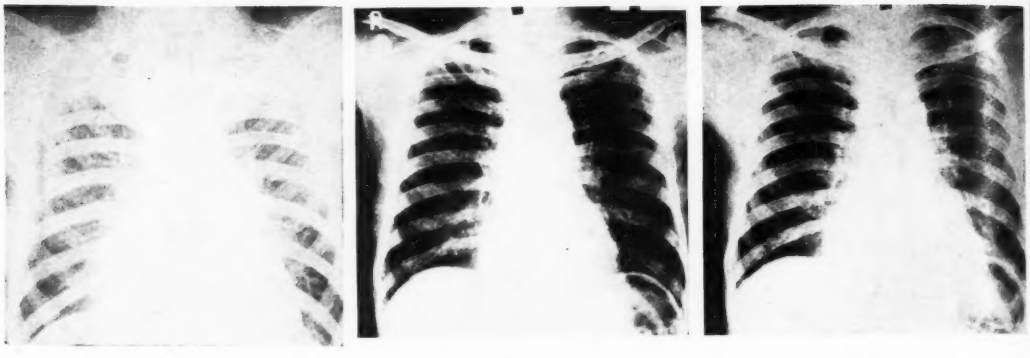


FIG. 3.—Serial electrocardiograms from patient referred to in legend to Fig. 2. Shows successive RS–T and T changes similar to those of subepicardial injury. Further discussion in text.
(A) 5/4/49. (B) 25/4/49. (C) 8/7/49, when electrocardiogram first became stabilized.



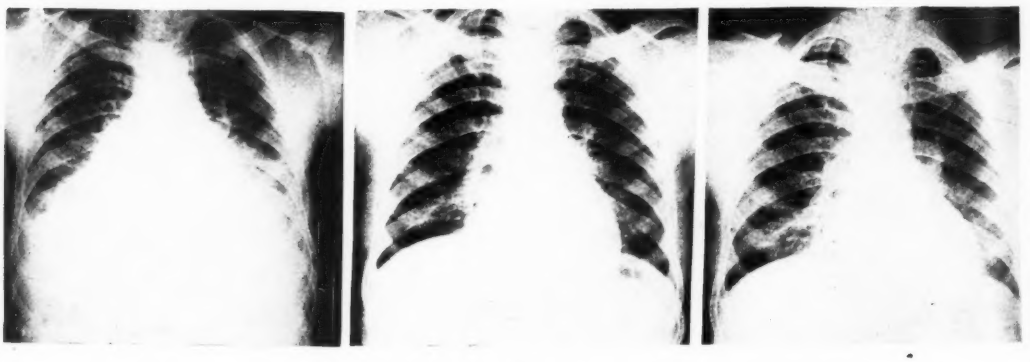
A B C

FIG. 4.—Man, aged 51 (Reference No. A21980).

(A) As on admission, 27/6/49. Congestive heart failure.

(B) 12/7/49. Heart size now normal. Has received no treatment other than standard diet. No signs of congestive failure at this stage. Weight loss 50 pounds.

(C) 23/7/49. Has been on restricted diet plus 25 mg. thiamin daily since 12/7/49. Venous pressure now raised. Recurrence of œdema. Increase in heart size.



A B C

FIG. 5.—Man, aged 31 (Reference No. A13677)

(A) As on admission, 21/4/49. Congestive heart failure.

(B) 3/5/49. Has been on standard hospital diet since 21/4/49. No systemic venous engorgement or œdema at this stage. Slight residual enlargement of heart which persisted subsequently.

(C) 21/6/49. Has been on restricted diet plus 10 grams of brewers' yeast daily since 10/6/49, when heart size was as in (B). Increase in heart size now apparent. At same time neck veins were engorged and œdema had reappeared over sacrum.

Corresponding electrocardiograms are shown in Fig. 6.

(*e*) Five patients were given 15 g. of brewers' yeast for 2–3 weeks without apparent benefit.

(*f*) Nine patients took 500–800 mg. of alpha-tocopherol daily for a period of not less than three weeks. Their clinical condition was unaffected.

(*g*) Three patients received 25 mg. of testosterone propionate daily for approximately 3 weeks without any beneficial effect.

These results show that when heart failure of this kind is not reversible by a wholesome diet alone no single drug or accessory food factor has yet been found substantially to augment the therapeutic value of that diet. Nor is there any evidence that curtailment of salt intake to an irreducible minimum does so.

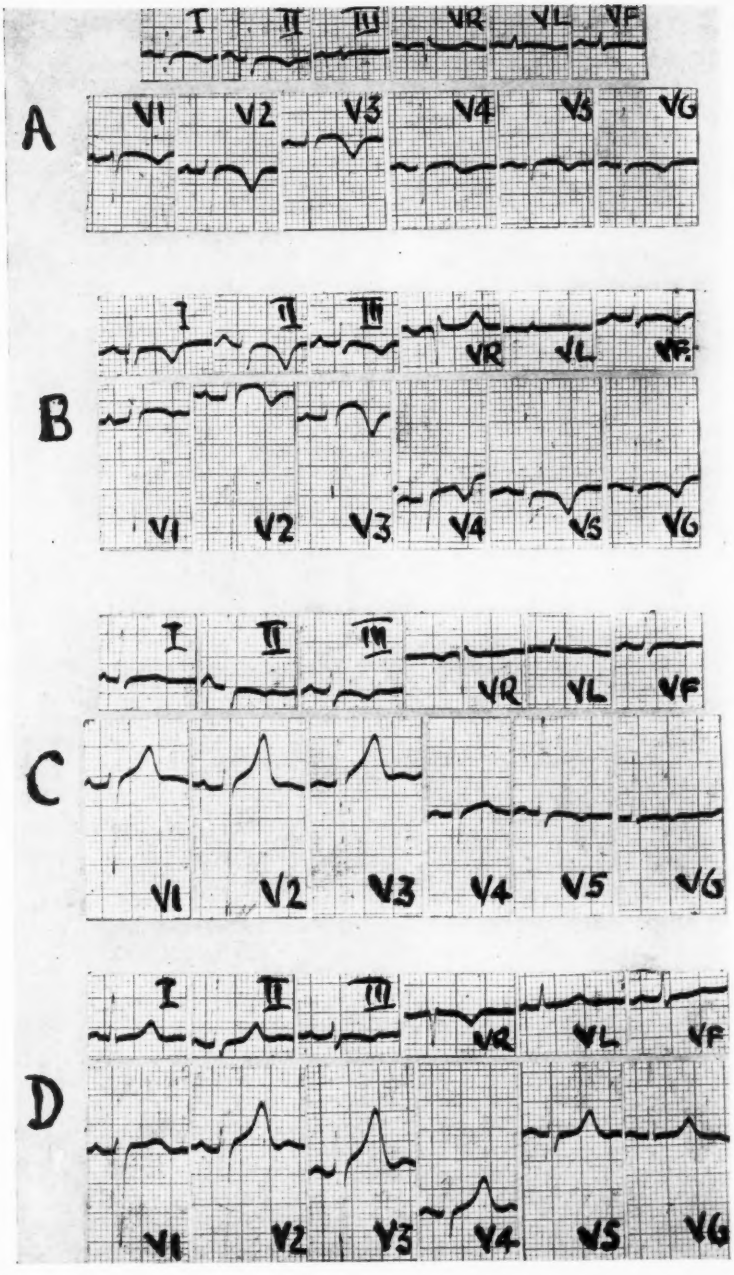
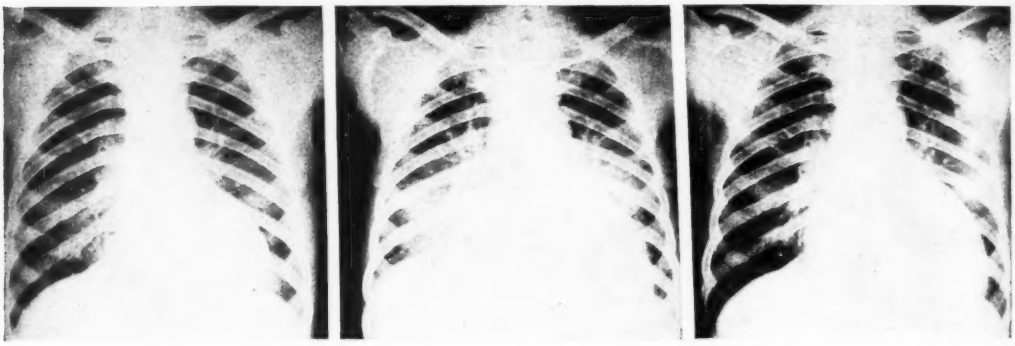


FIG. 6.—Serial electrocardiograms from same patient as referred to in legend to Fig. 5. The successive RS–T and T changes form the commonest cardiographic pattern in this form of heart failure. Further discussion in text.
(A) 21/4/49. (B) 4/5/49. (C) 22/6/49. (D) 1/8/49.

The eight patients who ultimately died were also treated with digitalis, mersalyl, aneurin, and alpha-tocopherol, either singly or in various combinations, without avail. Even so it would be premature to conclude that none of these drugs can in any circumstances be beneficial. Current studies are designed to discover the detailed effects of digitalis (and other drugs) on circulatory dynamics in this disease.

A further continuation of the dietetic experiments mentioned above is involuntarily provided by the patients' return to their own homes and habits. The results, however, are more difficult to assess because these people tend to migrate, especially after illness, and because most are still unwilling to return to hospital except when totally disabled. Of the twenty-two who were dis-



A B C

FIG. 7.—Man, aged 47 (Reference No. A19536).

(A) As on discharge from another institution on 14/6/49. Had been treated for congestive heart failure with digitalis, mercurial diuretics and ammonium chloride. Described as having recovered from congestive failure but heart remained enlarged.

(B) As on admission to this hospital on 29/6/49. Further enlargement of heart. Congestive failure.

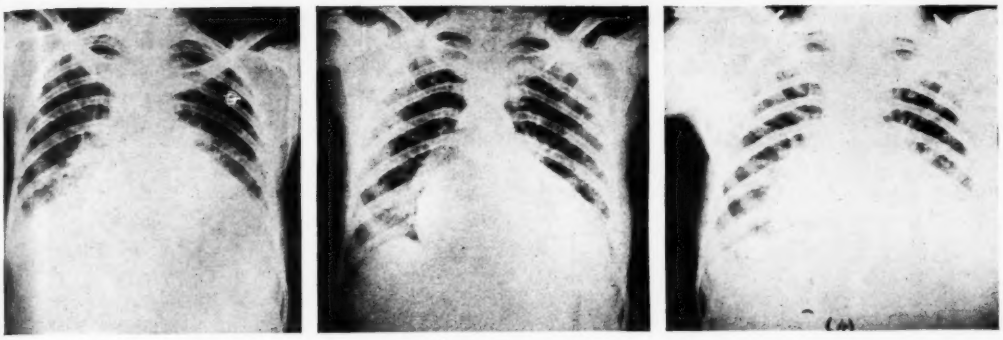
(C) 15/7/49. Has received no treatment other than standard diet. Diminution in heart size. Venous pressure has fallen but not yet normal. Slight residual œdema although weight loss 35 pounds. No further improvement obtained by digitalization, mercurial diuretics, aneurin or alpha tocopherol.

charged from hospital, twelve were traced subsequently. All had relapsed or, where recovery had not been complete, deteriorated. Among these the longest possible period of time that could have elapsed between discharge and increase in heart size, was eight weeks; between discharge and congestive heart failure or obvious deterioration, if recovery had not been complete, twelve weeks. Seven were re-admitted to hospital as emergencies in gross congestive failure, three of these within four weeks of discharge (Fig. 7 and 8). So far as was possible in the circumstances it could not be established that any of the drugs previously mentioned had any prophylactic value. An exception may be mersalyl. Three patients who had some œdema when discharged were prevailed upon to attend the out-patient department twice weekly for injections of this drug. In these it appeared that œdema increased less rapidly and by a less degree than in the remainder, but the drug did not prevent enlargement of the heart nor progressive increase in peripheral venous pressure.

DETAILS OF PROGRESS UNDER TREATMENT

So far as the cardiovascular system was concerned patients were classifiable into four grades according to their response to all treatment so far adopted.

(1) Where progress was optimum, as it was in nine patients, the most striking sign of recovery was an increase in the amplitude of cardiac pulsation as observed fluoroscopically. This was commonly seen in four to five days, invariably in the first week, and preceded apparent diminution in heart size. After a week or ten days the heart size was obviously smaller and in two to four weeks



A B C

FIG. 8.—Woman, aged 40 (Reference No. A2489).

(A) As on admission, 18/1/49. Congestive heart failure.
(B) 16/4/49. Maximum improvement since admission. Heart still greatly enlarged. At this time peripheral venous pressure was still raised and there was slight sacral œdema. This amount of improvement was obtained with dietetic treatment alone. Subsequently, digitalis, mersalyl, alpha-tocopherol, aneurin, and vitamin B complex, given singly or in appropriate combination, added nothing to this. The absence of significant pericardial effusion was confirmed by needling on three separate occasions. Patient discharged 30/4/39.
(C) Re-admission in congestive failure 15 days later.

normal (Fig. 1, 2, and 4). Gallop rhythm disappeared and the veins of the neck ceased to be engorged. Frequently in the phase of recovery there was a transient sinus bradycardia and an increase in systolic and diastolic pressures (Table III). These became stabilized at normal levels when recovery was complete. Urinary output increased, usually on the third or fourth day, and remained at a high level until the œdema subsided. The urinary excretion of chlorides increased at the same time. Weight loss in these circumstances varied in the nine patients from 34 to 62 pounds. Peritoneal and pleural effusions resolved less rapidly than subcutaneous œdema; sometimes they were aspirated to alleviate distress. Hydrarthroses subsided spontaneously in all instances before ascites or hydrothorax when these existed together; so did hydroceles. In two patients with bilateral hydrocele one side was aspirated and the other left untouched except for removal of 5 ml. of fluid for examination. The aspirated hydrocele did not recur in appreciable amount and the other subsided spontaneously at the same time as the anasarca. The protein content of hydrocele fluid from both sides was similar in each of these patients.

Probably the best guide to the total disappearance of œdema was a gain in weight following its precipitous decline. This was invariable. After this stage most patients continued to increase in weight during the remainder of the time that they were in hospital.

(2) Patients in the second grade were similar in so far as œdema disappeared but the heart remained slightly enlarged (Fig. 5 and 7). There were seven in this category and three of these had a permanently raised venous pressure. In two gallop rhythm persisted.

(3) Eight patients improved in every way but they failed to become œdema-free and their heart size, though substantially diminished, did not revert to normal (Fig. 8). Gallop rhythm persisted and peripheral venous pressure continued to be raised. It is equally characteristic of the second and third grades as of the first that arterial pressures rose temporarily during the phase of clinical improvement.

(4) In nine patients the circulatory failure was in all respects irreversible. They were gravely ill on admission but lived on for weeks or even months (and two still do) in a water-logged condition. The heart in all of these was enormous and virtually motionless when viewed fluoroscopically (Fig. 9). The œdematous tissues were indurated and pitted on pressure to a small extent only. It was confirmed at necropsy in six patients that this was due to cutaneous and subcutaneous fibrosis.

This was not confined to the most advanced stage of the disease for the same change, though in less degree, was demonstrated by biopsy in two patients from the third grade.

In all patients, including those who made a complete recovery from congestive heart failure, the liver remained enlarged, in most instances grossly so. The diminution in the size of the liver with subsidence of congestion was trivial; the recession of its lower border did not in any instance exceed 2 cm. The pain of liver distension, which was a prominent initial symptom, disappeared rapidly in all who improved, and from that time the palpable edge was hard, uniform and free from tenderness.

FIG. 9.—Man, aged 50 (Reference No. A295). Teleradiogram showing gross enlargement of whole heart; clear lung fields. Patient had advanced right heart failure, resistent to all forms of treatment. Pericardium was needled but no fluid located. Died subsequently with pulmonary congestion and œdema. Corresponding electrocardiogram shown in Fig. 10.

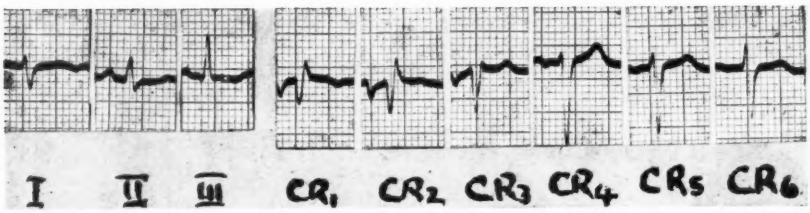


FIG. 10.—Electrocardiogram from patient referred to in legend to Fig. 9. At subsequent necropsy heart was found to weigh 750 grams. There was hypertrophy of both ventricles, chiefly of the right.

Statistically, plasma albumen and total protein (estimated per 100 ml. of plasma) increased during the time that patients were in hospital (Table IV). In the individual patient this increase did not correlate with the degree of improvement. The variation in plasma globulin during the same time was not significant but the trend of globulin values also was towards a higher level. It was usual for sensory loss to diminish and motor power to improve but deep reflexes were not restored. The only patient who had severe motor loss still had bilateral drop foot when discharged

four months later. He had prolonged treatment with aneurin but it could not be established that this vitamin had specific curative value (it did appear to stimulate appetite).

While in hospital eight patients developed sudden chest pain followed by hæmoptysis, presumably due to pulmonary embolism, which was not fatal in any instance. In two only was there radiological evidence of infarction and these had pulmonary congestion. In no case was there convincing evidence of peripheral venous thrombosis. Post-mortem findings in other patients indicated that the source of the embolus was ventricular mural thrombosis. Arterial embolism in one or more limbs occurred in three patients.

Mortality and Mode of Death

In this group of 30 patients eight died. One patient, after slow deterioration, died in apparent peripheral circulatory collapse. One, already seriously ill, died from massive pulmonary embolism which had its origin in a mural thrombus (this patient is not included in the previous reference to pulmonary embolism). Another patient, a middle-aged woman, after a most striking improvement, suddenly dropped down dead while sitting in a chair conversing amiably with her neighbour; the cause of this was not apparent at necropsy. Four died from progressive failure of the whole heart; a fifth in the same category was moribund on admission.

Notwithstanding the high mortality a more striking feature of this disease is the relatively long time that patients with enormous hearts and gross anasarca may live and even be ambulatory. It is characteristic of members of the Bantu race in this locality that they do not arrive in hospital before their disease is advanced in the extreme. With the single exception of the patient who died so unexpectedly after progressing so well, all who died had previously been in hospital on account of similar symptoms and were, when ultimately re-admitted, in chronic and (so far as is now known) irreversible heart failure.

Pathology

Necropsy. Post-mortem examinations were done on all patients who died but it is now realized that these were not sufficiently comprehensive to reveal the complex pathology of this disease. For that reason and because a detailed study of post-mortem material is now being undertaken a full account of the pathological anatomy will not be attempted at this stage.

In all instances the heart was greatly enlarged and its weight excessive; the walls of both ventricles were thickened. The heart valves were intact, the coronary arterial system and aorta not diseased. No convincing evidence of subendocardial necrosis or fibrosis was found in any (Bedford and Konstam, 1946; Davies, 1948). The amount of pericardial fluid was not significant from the point of view of producing either the clinical syndrome or the radiological appearance of the heart. Microscopically, there was inter-fibrillary œdema of the myocardium but no " hydropic " degeneration. Hypertrophy of muscle fibres in both ventricles was usual. Suitably stained sections showed minimal interstitial fibrosis.

The liver was enlarged in all and, though congested, fairly firm in consistency. In three patients it was obviously cirrhotic but in these, unfortunately, microscopic examination was omitted. In the remainder the histological features were those of hæmochromatosis (pigmentary cirrhosis or cytosiderosis with cirrhosis of Gillman and Gillman, 1945). In some instances (it was not looked for in all) the same change affected other organs such as the pancreas and spleen, but not the heart.

The lungs of all were congested but without primary disease. Pulmonary infarction was found in one patient and splenic infarction in another. In these, ante-mortem thrombus was adherent to the endocardial surface of the right and left ventricle respectively. Nephrosclerosis was excluded in all.

Liver biopsy. Needle liver biopsy was done on all patients who survived (22). This minor operation was undertaken only after maximum recovery from congestive failure. No untoward effect occurred in any case. Apart from chronic venous congestion and its sequelæ, which were observed

in four specimens, all biopsy sections showed disease of the liver. In nineteen the salient lesion was cytosiderosis (Fig. 11). Of ten in which the siderosis was both intra- and extra-cellular there was portal fibrosis in seven; of nine in which it was intra-cellular only there was portal fibrosis in four. In three patients the only lesion revealed by biopsy was fatty change. In eleven this co-existed with hæmochromatosis. Round cell infiltration of the portal tracts was a common accompaniment of the other lesions mentioned.

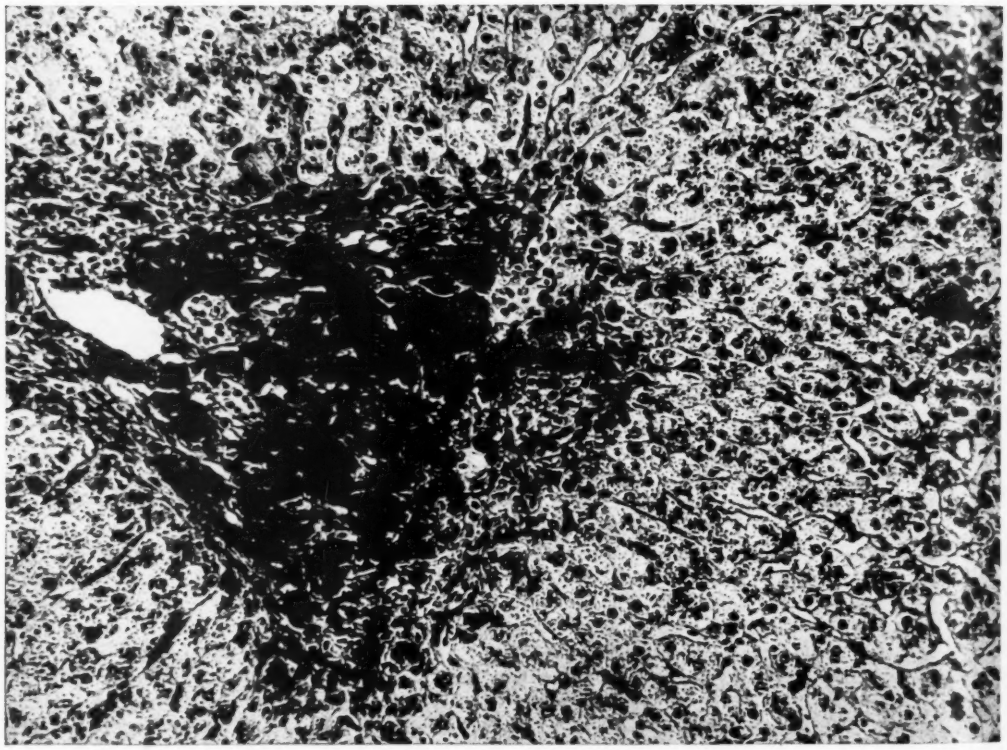


FIG. 11.—Man, aged 34 (Reference No. 16434/48). Cf. Fig. 1, which refers to same patient. Needle biopsy of liver showing portal fibrosis and round cell infiltration. There is also deposition of hæmosiderin which is visible not only in the liver cells but as a very heavy deposit in the portal tract and in the Kupffer cells of the sinusoids. H & E and Prussian Blue reaction. × 210.

DISCUSSION

The syndrome of œdema. Irrespective of the detailed mechanism, congestive heart failure constitutes a valid cause of œdema. Nevertheless, the œdema that has been described differs in some respects from cardiac œdema. In degree it was, almost without exception, extreme. Its distribution on the body surface was generalized. More than 40 per cent of all patients had hydrarthroses and 20 per cent had bilateral hydrocele. That in individual patients these effusions behaved in the same way as the effusions known to be dropsical suggests that they had a common cause. The protein content of the joint and hydrocele fluids was compatible with this interpretation. Notwithstanding its widespread distribution, however, the œdema was always greater in the dependent parts of the body than elsewhere. As the œdema subsided it first disappeared from the face and lastly (in the

recumbent patient) from the soft tissues overlying the sacrum. The accumulation of œdema, according to Burch and Winsor (1944), is restrained by the elasticity of the skin. It is no doubt true, although it has not been proven in this group of patients, that poor nutrition causes a diminution of tissue elasticity.

Malnutrition and disease of the liver are both potential causes of œdema. In each case the protein content of the œdema fluid is substantially less than it is in œdema of cardiac origin (Peters and Van Slyke, 1932; Bodansky and Bodansky, 1944). It will presently be argued that, in the patients now under discussion, chronic malnutrition was the cause of heart failure; liver disease was shown to co-exist in every instance. Yet the protein content of œdema fluid from the various body cavities and subcutaneous tissues, estimated admittedly in only a small number of patients, did not differ significantly from that reported elsewhere in congestive heart failure of other ætiology (Gilligan, *et al.*, 1934; Bramkamp, 1935; Fishberg, 1940). Only in three patients were plasma albumen levels less than 3·0 g. per 100 ml., the reputed "critical level" for nutritional œdema (Bruckman and Peters, 1930). It is unusual for ascites to develop in hepatic disease unless the serum albumen falls below 2·5 g. per 100 ml. (Higgins *et al.*, 1947). In the present series albumen levels less than this were recorded in two patients only, yet ascites was clinically apparent in twenty-seven. Neither plasma albumen nor total protein values correlated with the degree of œdema preceding treatment nor with the residual œdema where recovery was incomplete. According to Starling's concept of a balance between the oncotic pressure of the plasma and the hydrostatic pressure of the blood in the capillaries (Starling, 1896) any reduction in plasma protein, especially in the albumen fraction, will tend to cause an accumulation of fluid in the tissue spaces. Apart from that there is, in the present instance, no positive evidence that hypoproteinæmia played a greater role in the genesis of œdema than it does in congestive heart failure of other kind (Payne and Peters, 1932). It would be helpful in this respect to know the circulating blood volume. This is said to be increased in all forms of congestive heart failure, largely by reason of an increase in corpuscular volume (Meneely, and Kaltreider, 1943). Hæmatocrit readings in our patients were too few to permit of reliable comment but hæmoglobin (and r.b.c.) values were strikingly normal. These, however, were recorded once only, when the patient first came under observation. Levels of plasma albumen and also of plasma globulin rose over the period of clinical improvement. It may well be that this reflects a falling blood volume during recovery from congestive failure.

Comment on differential diagnosis. Because this disease has frequently been labelled hypertensive heart failure in the past, care has been taken to exclude any with established hypertension from the series now reported. Systolic and diastolic pressures did increase in most patients in the phase of recovery but these pressures subsequently returned to normal levels. Furthermore, although there is good reason to believe that heart failure of other ætiology is frequently precipitated by malnutrition, and the pattern of failure modified by it, all with any other potential cause of heart failure were excluded. Notwithstanding the wide range of plasma cholesterol there was no evidence of thyroid disease in any instance. The basal metabolic rate, recorded in those patients in whom plasma cholesterol deviated most from the mean, bore no relation to the cholesterol level. The mean plasma cholesterol was low. So far as a single recording has any significance this may be an index of chronic malnutrition (Man and Gildea, 1936) or liver failure (Peters and Van Slyke, 1946). Of greater import in this respect is the fasting hypoglycæmia, a known accompaniment of advanced hepatic disease (Judd *et al.*, 1934; Moore *et al.*, 1934; Conn *et al.*, 1938). The syndrome that is now reported cannot be identified with Van Gierke's disease but glycogen metabolism has yet to be studied in detail. No significance could be attached to serum potassium levels in determining the pattern of the electrocardiogram.

Etiology. Recent surveys have disclosed the prevalence of malnutrition in the non-European community of this country (Fox, 1934, 1939; Brock and Latsky, 1944; Dugard, 1945). Gillman and Gillman (1945) have shown that in the malnutritional syndrome of these people liver disease is invariable; fatty infiltration, cytosiderosis, and cirrhosis, though not necessarily consecutive lesions, are patterns of liver reaction to the injury of prolonged malnutrition. They distinguish two

phases of cytosiderosis. In the first phase iron pigment appears in the liver cells and little or none in the Kupffer cells; in the second iron is additionally deposited in the Kupffer cells and portal tracts (Gillman and Gillman, 1947). Cirrhosis and fatty change, or either alone, may co-exist in either phase. All patients now reported had liver disease of this kind; all stages of the disease were manifest. The comprehensive histological diagnosis in most instances was pigmentary cirrhosis that is indistinguishable from hæmochromatosis.

Because people known to be malnourished develop heart failure that otherwise cannot be explained, it does not follow that malnutrition is the cause. Nor does this necessarily follow because they recover when given an adequate diet at the same time as they are confined to bed in hospital. But the development, under the same controlled conditions, of cardiac enlargement and failure when the diet is restricted to the patients' accustomed fare (albeit that this observation was not frequently repeated) is strong evidence that the deficient diet and not some positive environmental factor is immediately responsible. Gillman (1944), in his investigation of nutritional liver injury, fed rats on a diet comparable to that of the South African Bantu. The rats developed fatty infiltration of the liver which in many instances progressed to cirrhosis. It is noteworthy that these rats' hearts became greatly enlarged.

The hepatic lesion that has been shown, without exception in the present investigation, to accompany cardiovascular disease is irreversible. In contrast, cardiac enlargement and failure, of moderate or even severe degree, are reversible—under the influence of wholesome food alone. There is a distressingly high incidence of malignant malnutrition (kwashiorkor) among Bantu children; in that syndrome the liver is always fatty (Gillman *et al.*, 1944; Altmann, 1948). The diet of the patients now described has been deficient from the time that they were weaned. The presumption is that the syndrome portrayed in the adult dates from childhood.

It is indisputable that for a long time the heart remains functionally intact despite deficient diet. Its ultimate failure is understandable as a cumulative effect of prolonged malnutrition. On the analogy of other nutritional diseases the ready recovery from congestive failure and the diminution in heart size when the dietary deficiency is made good substantiates this interpretation. What is less easily understood in these circumstances is the rapidity with which heart failure recurs in the successfully treated patient when his diet is again restricted. Clearly the heart has become " sensitized " in some way to the influence of inadequate food intake. It may be that a salutary role in the nutrition of the heart is exercised by the liver; that the heart fails when the liver, because of its own progressive injury, can no longer function in this way.

Isolated deficiencies. Gynæcomastia, which is an index of malnutrition in the African, is reputed to be due to failure by the liver to inactivate œstrogens (Davies, 1949). It was the frequency of this and other signs of feminization that prompted the use of testosterone as a therapeutic agent. It had no beneficial effect. In the experimental animal tocopherol deficiency causes (among other things) degenerative changes in the testes and myocardium (Mason, 1926; Mason and Emmel, 1945); progressive cardiographic abnormalities have been reported by Gullickson and Calverley (1946). Tocopherol protects the animal liver against the injurious effects of a diet deficient in thioamino acids (Schwarz, 1944). These facts constitute the rationale for the therapeutic trial of alpha tocopherol. Strikingly favourable results in the treatment of cardiovascular disease with this vitamin have been reported by Vogelsang, Shute and Shute (1948) but no benefit accrued to any of our patients treated in this way. Apart from the association of aneurin deficiency with cardiovascular failure (Follis *et al.*, 1943) it is of interest that three of four dogs rendered pyridoxine-deficient by Street, Cowgill and Zimmerman (1941) developed signs of congestive heart failure and died suddenly. Neither aneurin nor whole vitamin B had any curative or prophylactic value in the type of heart failure now under discussion.

Inanition alone, as distinct from qualitative defects of diet, causes some change in most organs. Although these have no specificity they are continually being attributed to deficiencies of single nutrients (Follis, 1948). Notwithstanding the absence of vitamins from the Bantu diet the classical avitaminoses are rare.

It may be that deficiency of a single food factor is the cause of heart disease in the South African Bantu. Investigation of this possibility is being continued; at present, attention is being directed to the essential amino acids that are lacking from maize protein. Nevertheless, less emphasis should be laid on the ultimate components of diet than on the provision of wholesome table food.

Summary

A form of congestive heart failure, believed not to have been previously described, that occurs in African adults, has been observed. The clinical syndrome and the ætiology of the condition have been studied in 30 cases.

Apart from the common signs of congestive failure outstanding clinical features were (*a*) enlargement of the whole heart which, on fluoroscopy, was typically inert, (*b*) the constancy of gallop rhythm, (*c*) the extreme degree of œdema, and (*d*) the co-existence of disease of the liver.

The diet of all patients was, quantitatively and qualitatively, deficient. In five patients who willingly subjected themselves to the trial it was shown that once heart failure of this kind had developed it progressed, even under optimum environmental conditions, so long as they continued to subsist on their accustomed diet.

In all but the most advanced stages of the disease heart size diminished and signs of failure retrogressed when a well balanced diet was substituted for the deficient one. Not only did the disease relapse when patients left hospital and reverted, inevitably, to their previous diet, but cardiac enlargement and failure readily developed in six convalescent patients under controlled conditions when their diet was restricted to their habitual fare.

When the disease has been long established enlargement of the heart and congestive failure become irreversible.

No drug or single food factor has been found to augment the curative value of wholesome food or to have any prophylactic or therapeutic value in face of the deficient diet on which these people have to live. Mercurial diuretics may be useful in controlling œdema in the more chronic phase of the disease. Aneurin is no exception to this statement.

This syndrome of heart failure does not clinically resemble that due to beri-beri, and there are none of the features of a hyperkinetic circulation.

In the African, fatty infiltration of the liver, which may be fatal or progress to cytosiderosis or cirrhosis or both, is caused by prolonged underfeeding on a diet identical with that of the patients discussed in this paper. One or other variant of this liver lesion was found in all cases.

For a long time, notwithstanding deficient diet and progressive liver injury, the heart remains free from gross disease. When the heart has once failed and recovered under treatment, it will readily fail again under the influence of the same deficient diet, even though recovery had seemed complete. It may be that in circumstances of continued underfeeding, a function of the liver is to ensure optimum nutrition of the heart; that ultimate failure of the heart, although a consequence of malnutrition, may be conditioned by primary failure of the liver.

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FIRST EFFORT ANGINA

SECOND WIND IN ANGINA PECTORIS

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The ability of certain patients subject to angina pectoris at the beginning of a particular effort thereafter to undertake further and even greater exertion without pain has been recognized since Heberden's time, and was compared by Wenckebach with the " second wind " of athletes. My attention was first directed to this phenomenon by three striking examples, in which strenuous athletic activity, squash racquets, ice hockey, and fencing, could be carried on after initial difficulty due to angina pectoris. With interest thus aroused it was found that the condition is by no means uncommon.

A search yielded many brief references and three more detailed contributions—Gallavardin, 1925, Wenckebach, 1928, and Wayne and Graybiel, 1934. The earliest found was the letter to Heberden from an unknown gentleman (Heberden, 1785) who wrote: " I have frequently, when in company, borne the pain, and continued my pace without indulging it; at which times it has lasted for five to perhaps ten minutes, and then gone off, as well as I can recollect, rather suddenly, as it came on, than lessening gradually." It is mentioned by Trousseau (1881), and Osler (1897) quotes one patient who assured him that in moderate attacks on the street, by a strong effort of will he could continue to walk and the pain gradually subsided. Verdon (1910) reported: " After several breaks in the journey, and when gastric distension had been relieved by repeated eructations of flatus, a considerable length of road might be transversed without the occurrence of any further manifestations of thoracic discomfort." Allbutt (1915) quotes a case of Parry's, but states that in his own experience stillness had been invariable. Mackenzie (1916) considered the phenomenon remarkable and regarded it as evidence that " in these hearts a good deal of healthy muscle is present and that the attacks of distress are provoked by the introduction into the picture of some factor which is not myocardial weakness—for example, a full stomach."

Gallavardin (1924 and 1925) described the condition briefly and introduced the term " mise en train difficile." In his monograph (1925) he described it more fully, stating: " Many subjects say that their attacks come much more easily, sometimes almost exclusively at the beginning of their outings; they stop several times for example in the first 500 to 600 metres, then later, ' when they have warmed up,' they say walking becomes easier." He contrasts it with dyspnœa of effort which shows no such vagaries. He suggested that subjects of angina have a mechanism which is slow to adapt itself, as if things were a little stiff or rusty, and that exercise loosens them up. He felt that this fitted in well with coronary spasm. He cites another of his patients who experienced a severe attack of angina while hunting: not wishing to give in, he had, at the price of severe pain, continued and was very surprised to feel the pain go suddenly; this was followed by profuse sweating. Gallavardin remarks that such sweating, which he had noted in another patient, is never seen with attacks of dyspnœa occurring on effort, and that such a sudden termination favours the cessation of a spasm. A final point in favour of angiospasm is the marvellous efficacy of the vasodilators, notably nitrites, in the relief of attacks.

Wenckebach (1928) wrote an article with the title " Toter Punkt, Second Wind, und Angina

Pectoris." For the translation of " toter Punkt " I am indebted to Dr. Parkes Weber who renders it " dead point," but thinks there is no exact English equivalent. This is the moment when the untrained runner feels like dying, before the relief of the " second wind " comes. Wenckebach describes the strange oppression noticed at the onset of a major physical effort. This " initial inhibition " is only of very short duration. If the activity is continued, sometimes consciously or unconsciously at a more leisurely rate, this oppression disappears; this relief, after the " first wind " seemed to have spent itself, is called " second wind." The initial inhibition may be so strong that the effort must be discontinued; the " toter Punkt " (dead point) is reached, and can only be overcome by a short rest or forced effort. He believed the physiological mechanism to be as follows. The beginning of exertion brings about an increased blood flow to the heart which originates chiefly in the venous splanchnic bed, but most important is that apparently the blood flow from the central arteries to the periphery and into the veins is at first still blocked—a mechanism that causes even under physiological conditions a phase of arterial mainly aortal engorgement. He states that nitrites will interrupt this initial phase and so forestall the development of " toter Punkt." He goes on to say that an attack of angina shows a complete analogy with these features. Following Allbutt's hypothesis he believed the pain to be due to distension of the aorta and larger arteries by raised blood pressure due to peripheral vaso-constriction. The pain in turn further raised the blood pressure causing a vicious circle.

Sutton and Lueth (1930) suggested " that the anatomically normal heart may, under conditions of extreme exertion, fail to receive sufficient blood (nutrition) through normal coronary arteries. In fact, this is suggested in the sensation of athletes just before " getting their second wind." They remark upon the surprising similarity between the sensations of an extreme effort in youth and of angina pectoris in later life, and quote " the unsolicited observation of a patient that the sensation felt as a young man after running up a mountain side during an emergency, was exactly the same as that now felt thirty years later during an attack of angina pectoris."

Lewis (1932) advanced the view that the pain in muscular ischæmia is due to a substance that develops in the tissue spaces around the muscle fibres and accumulates when there is oxygen lack. He quotes the letter to Heberden and adds: " That is a phenomenon difficult to explain by a simple basis of pressure and rates, but is easy to understand if it is believed that the coronary circulation accommodates itself gradually to the condition of exercise." He considered coronary constriction the most important factor.

Wayne and Graybiel (1934) in an important paper reported the results of investigation into the effect upon exercise tolerance of food, distension of the stomach, external temperature, and repeated exercise in patients suffering from angina pectoris. They used a two-step exercise and counted the number of efforts required to produce pain under various conditions. Two of their cases showed increased tolerance on repeated exercise. In one of these the initial number of efforts was 58; fifteen minutes later 116 efforts were performed before pain occurred. They found a diminution of tolerance if a second attempt was made within two minutes of the first, and in most cases exercise tolerance was unaltered when fifteen minutes rest was given.

Brief references are made by Cowan and Ritchie (1935), Levy (1936), and Levine (1945). Bramwell and King (1942) mentioned the term " second wind " and suggested that coronary dilatation might play a part in this adaptation which was considered to be a favourable omen in prognosis.

Patterson, Clark, and Levy (1942) observed cardiographic changes suggestive of a similar adaptation during the " anoxæmia test " in certain patients with coronary sclerosis. " In many of the cases of coronary sclerosis the total RS–T deviation increased in linear fashion as the test progressed. In some, the degree of deviation rose to a peak and then decreased. The latter sequence of events suggested that compensatory mechanisms in the circulation had brought about a favourable adjustment in coronary flow. One of the methods of adaptation appeared to be an increase in pulmonary ventilation." Bedford (1943) quotes the case of a doctor with angina pectoris who, in order to work in comfort, deliberately provoked his pain by cranking up his car so as to get it over before starting his morning round.

The Present Series

This consists of twenty patients who showed this phenomenon. All were believed to be suffering from coronary sclerosis. A supplementary case showed a similar condition during paroxysmal tachycardia.

Incidence. There has been considerable difference of opinion as to the frequency with which " second wind " occurs in patients subject to angina pectoris. Allbutt (1915) had never seen a case personally. Cowan and Ritchie (1935) and Lewis (1933) considered it rare. Gallavardin (1925) regarded the phenomenon as common but a forced stop as more usual; he said that if asked many patients described it. Wenckebach (1924) stated that it was " by no means uncommon," and Mackenzie (1916) referred to " many people " who have difficulty in starting from rest. Wayne and Graybiel (1934) as a result of their experiments concluded that in angina of effort there is usually a phase of increased exercise tolerance, but, as this is often short, it is difficult to demonstrate clearly.

The condition is certainly noted more often when the possibility is kept in mind during the interrogation. Not all patients who have experienced " second wind " will volunteer the information in a routine history, and without a specific question on this point cases will frequently be overlooked. If deliberate enquiry is made from all patients with cardiac pain a positive answer may be obtained as often as once in every five cases.

Age, Sex, and Occupation. The youngest was 33, and the oldest 73 years old. Fifteen were between 50 and 70. All were men. This does not differ significantly from the expected findings for angina pectoris. Occupation was varied and in no way remarkable.

Effect of Tobacco. Of 13 patients questioned about this, 4 were non-smokers, 8 smoked moderately, and 1 heavily.

Hypertension. Taking 165/100 mm. Hg as the upper limits of normal, a third of the patients in the series was hypertensive. Though previous hypertension may have been reduced in some by cardiac infarction, all except three of those with normal blood pressures had normal-sized hearts on radioscopy. Of the three exceptions two had suffered posterior cardiac infarction and the other had aortic incompetence.

Need for Rest Pause. Some patients stop once, twice or more soon after setting out, others carry on without stopping. The strong effort of will required by the latter has been mentioned by Osler (1897), Parry quoted by Allbutt (1915), Gallavardin (1925) and Wenckebach (1928). The difference appears to be in the patient's character. Those of a strong and determined nature will endure more pain temporarily in order to walk it off. Others are content to pause a few times until adaptation has occurred and they can move freely without pain.

Time of Day. Some patients are conscious of difficult starting only in the morning and not later in the day. Mackenzie (1923) pointed out that " during sleep the output of the heart is at its minimum, and the heart muscle requires like the other organs a minimum supply of blood. He suggested that this might be due to some of the capillaries having closed down during rest. Gallavardin (1924) thought " mise en train difficile " tended to occur more in those whose pain was worst first thing in the morning. Bedford (1943) mentions the " first walk of the day " and Levine (1945) cites those who " may have a spell going to the train after breakfast and be free for the rest of the day."

One patient volunteered: " After the first hole I don't get it again." Another stated: " On going out to golf after breakfast at 9 a.m. on the first two holes I felt pain at mid-sternum, and then it went off after playing the third and subsequent holes. It vanished." The occurrence of pain during the first hole or two of a round of golf has been frequently observed (Levy, 1936; Levine, 1945; and six cases in this series).

The Part Played by the Stomach. It has been suggested that in " second wind " the gastric factor may be of greater importance than it is in ordinary angina of effort. Mackenzie (1916) thought that " the attacks of distress are provoked by the introduction into the picture of some factor

which is not myocardial weakness—for example, a full stomach." Relief from belching was mentioned by Verdon (1910) and was mentioned voluntarily by four of this series. In those who notice the pain particularly when starting after breakfast (three cases), both first effort of the day and a full stomach may have played a part. Wayne and Gabriel (1934) found that exercise tolerance in patients suffering from angina pectoris of effort was diminished after food but not after distending the stomach with air. One of their cases with spontaneous pain also got it on distension with air. This was thought to be due to vasomotor changes reflexly from gastric distension.

Gilbert *et al.* (1940) produced some experimental evidence that in dogs distension of the stomach reduces coronary flow, but Wiggers (1944) commenting on this work considered that the conclusions " cannot be accepted as indisputable." Of the subjective relief in certain cases after belching there can be no doubt.

Effect of Nitroglycerine. Wayne and Graybiel (1934) found that nitro-glycerine increases exercise tolerance considerably in all cases showing this phase of increased tolerance, and concluded that a previous attack of angina acts similarly to nitroglycerine although in each case a greater effect is produced by the drug. In two cases showing no raised exercise tolerance they suggested that the coronary circulation remained unaltered during exercise, for the exercise tolerance of one was unaffected and the other only slightly increased by nitroglycerine in full doses.

In this series it was found that the difficult start could sometimes be prevented by a prophylactic dose of nitroglycerine (three cases).

Prognosis

The prognosis in patients showing " first effort angina " has been thought by some to be particularly favourable (Mackenzie, 1916; Bramwell and King, 1942).

Consideration of the present series does not support this view. In only one could the electrocardiogram be passed as normal. One showed slight widening of QRS complexes and a QIII. Five showed R–T deviations. Six had abnormal T wave inversion. In seven there was a clinical history suggestive of coronary thrombosis, and in one of these " first effort pain " started a fortnight before an extensive anterior infarction from which the patient died a fortnight later.

In some it appeared as an early symptom—pain only when playing the first hole or two of golf would after weeks or months give place to pain all round (three cases). The most striking example was a patient who played in ice hockey matches without pain after the first five minutes, and he had never had pain at rest. His electrocardiogram, however, showed T wave inversion in all the unipolar præcordial leads which took months to recover. " First effort pain " sometimes followed cardiac infarction (three cases) or was followed by cardiac infarction (five cases). It may be that the cardiologist tends to see the more severe cases of angina pectoris, and it is possible that many patients with pain confined to first effort may not seek medical advice, or even if they do so may not be referred to a consultant. There is no proof of this, however, and I have found no evidence that the prognosis of " first effort angina " is any different from that of angina of effort generally.

Mechanism

It would probably be agreed now that " second wind " in angina pectoris is due to some form of adaptation of the coronary circulation to exercise. It is in attempting to determine more exactly the mechanism involved that difficulties are encountered. Lovatt Evans (1949) writes, " Despite its importance, we are still in doubt regarding many aspects of the coronary circulation as it operates in the normal heart in the intact chest, since nearly all available methods of experiment introduce some abnormal factor of incalculable effect."

Coronary spasm was suggested by Gallavardin (1925). Parkinson and Bedford (1931) from their observations on the electrocardiogram during brief attacks of angina pectoris, took the view that coronary spasm does in fact occur in angina pectoris, and suggested that narrowing of a main coronary branch might predispose to spasm of the arterioles that spring from it. The

rapid reversal of T wave inversion by nitroglycerine sometimes seen in spontaneous angina (Kemball Price and Janes, 1943) and the cardiographic changes that come and go during smoking (Wilson and Johnston, 1941) provide further evidence of the existence of coronary spasm. Lewis (1932) believed coronary constriction to be the most important factor in difficult starting.

Failure of the coronary arteries to dilate rather than spasm was suggested by Sutton and Lueth (1930). Greene (1931) demonstrated that in the dog the coronary constrictor reactions are very small compared with the coronary dilator reactions, and he suggested that " during coronary sclerosis, and during the period of loss of coronary resilience preceding massive sclerosis, the arteries are less constricted by reflex constrictor nerve impulses, in fact cannot be thrown into spasm because of the rigidity and non-resilience. On the other hand, neither can such vessels respond to reflex coronary dilator reactions, hence they do not, in fact cannot, increase the blood supply under the very conditions that greatly augment the work of the heart.

Coronary dilatation as the cause of " second wind " as suggested by Wayne and Graybiel (1934) and Bramwell and King (1942) is not incompatible with a preceding coronary spasm. It is also consistent with a failure to dilate if the rigidity is in the larger arteries and the dilatation is confined to the arterioles. That a similar phase of increased exercise tolerance occurs in some patients with intermittent claudication has been stated by Ratcliffe (1949) and was observed in one case in this series. According to Allen, Barker, and Hines (1947) the arterioles in extremities afflicted by arteriosclerosis obliterans are in a condition of normal tone most of the time, thus they are susceptible to either vaso-dilatation or vaso-constriction.

It would appear that in patients with " first effort angina " there is some delay in coronary dilatation at the beginning of exercise. The important influence of mean aortic pressure on coronary flow is well established (Wiggers and Cotton 1933). Wiggers (1923) had already shown that the height of the blood pressure, as a rule, overbalances active vasomotor changes. Thus, if a general vasoconstriction, in which the coronary vessels partake (for example after adrenalin) is induced, and the blood pressure is raised in this way, the flow through the heart will increase. It is conceivable that narrowing of the larger coronary arteries from atheroma might not only predispose to spasm of the arterioles, but might prevent sufficient head of pressure being developed to overcome their spasm or constriction. " Second wind " might occur when the arterioles dilate independently.

Summary

First effort angina may be defined as that which develops soon after a particular effort begins, but disappears despite continuation of that effort. A brief pause or curtailment on account of the pain is usual but not invariable, and thereafter the particular effort may be completed or even extended without further discomfort. This form of angina pectoris has been compared in respect of pain with " second wind " in respect of dyspnœa. A series of 20 patients who showed the phenomenon was collected and analysed, and the subject is discussed.

First effort angina is fairly common. Few patients with angina describe it voluntarily, but if questioned one out of five may admit that they have experienced this modification of it.

No evidence has been found to suggest that the prognosis differs from that of angina pectoris generally. In course of time it gives place to the usual form which compels relinquishment of the effort.

It is possible in a proportion of cases to prevent the first effort pain by nitroglycerine taken before starting.

It seems likely that the difficult start is due to failure of the coronary arterioles to dilate soon enough on first effort. Narrowing of a large coronary vessel from arterial disease might predispose to transient spasm of the arterioles it serves, and might also tend to reduce the influence of the rise of aortic pressure at the beginning of exercise on coronary flow.

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ELECTROCARDIOGRAPHIC STUDIES DURING OPERATION FOR COARCTATION OF THE AORTA

BY

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Considerable attention has recently been focussed upon the disturbance of cardiac rhythm that may occur during intrathoracic surgery (Meek *et al.*, 1937, and Burstein, 1946). These arrhythmias may vary from the relatively innocuous nodal rhythm and shifting pacemaker to cardiac standstill and ventricular fibrillation. Several initiating factors have been described, among which are cyclopropane anæsthesia, endotracheal intubation, cutting and spreading of ribs, hilar stimulation, opening of the pericardium, and dislocation of the heart (Burstein, 1947). The mechanisms by which such abnormal cardiac action has been brought into play have not always been clearly defined. In certain cases increased vagal tone or direct vagal stimulation has appeared to be the most probable cause. The work of Sloan (1949) showing the increase in vagal sensitivity with anoxia has shed considerable light on this. It seems clear then that hypoxia and hypercapnœa play a very important role in precipitating these abnormalities, whether mediated through a vagal mechanism or not.

Surgery for coarctation of the aorta has been complicated by the occurrence of several serious disturbances of cardiac function during or shortly after operation (Shapiro, 1949, and Clagett, 1949). In 100 operations reported recently by Gross (1950), there appeared to be three phases of the operation during which cardiac irregularities are especially apt to occur. The first is during the period of hypertension following the clamping of the aorta. This has proved even more hazardous if the subclavian artery also has been occluded. One patient died three days after operation and necropsy showed cerebral hæmorrhage; both aorta and subclavian artery had been clamped off during aortic anastomosis, and it is believed that the resultant excessive hypertension caused the cerebral hæmorrhage. Another patient had severe convulsions during this phase.

The second danger point proved to be immediately after the release of the aortic clamps. One patient died suddenly at this juncture, and temporary cardiac arrest occurred in three, and shock in several more. Other surgeons are known to have encountered difficulties of similar nature at this point.

The end of the operation marks the third phase that has been associated with a number of cardiac disturbances. Two patients developed severe shock at the end of operation and subsequently died.

Only one patient, who developed marked pulmonary œdema and died shortly after the opening of the chest, showed a severe disturbance of cardiac function at an interval unrelated to the three just mentioned.

Many of these accidents were quite unrelated to vagal reflexes. Shock and death on release of the aortic clamps were probably due to rapid change in hemodynamics effected by sudden removal of peripheral resistance added to previous blood loss. Shock following cyclopropane

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anæsthesia was apparently due to the factors brought into play under long use of that agent, namely, sustained blood pressure in spite of marked blood loss, followed by sudden fall of blood pressure when the anæsthetic is removed (Dripps, 1947).

Both these shock-like reactions have subsequently been avoided by slow removal of aortic clamps, more adequate replacement of blood loss, and the use of ether instead of cyclopropane anæsthesia.

The cerebral hæmorrhage and convulsions noted were not accompanied by recognizable arrhythmias but, in themselves, may be interpreted as being manifestations of an overloaded cardiovascular system. Prevention of such reactions has been attempted by keeping the blood pressure below excessive levels: this has been accomplished by delayed replacement of blood until the maximum rise in blood pressure has passed.

Although the above explanations have served as practical guides, more accurate analysis of cardiac activity was indicated for better understanding of abnormal heart action during operation. It seemed especially important to find out whether the clamping of the aorta, or the subsequent release of the clamps, had any specific effect on the cardiac rhythm. The present study was consequently undertaken of the electrocardiogram during operation for coarctation of the aorta.

Clinical Material and Method

Ten cases of coarctation of the aorta form the basis of this study. In all instances, the pre-operative diagnosis was well established by the usual diagnostic criteria (Reifenstein *et al.*, 1947). Seven were males and three females. They ranged from 11 years to 35 years of age, with an average of 18 years.

All were operated upon by Dr. Robert E. Gross during the period from January to September, 1949. In 7, excision of the stenosed portion of the aorta followed by end-to-end anastomosis (Gross, 1945) was done; the other 3 necessitated vascular grafting (Gross, 1945) in view of the unusual length of the coarctation. All of them tolerated the operation satisfactorily. However, Case 3 developed renal failure post-operatively with oliguria, further rise of blood pressure, mental disorientation, and terminal pulmonary œdema: this complication was presumably caused by excessive sodium being given inadvertently, and necropsy showed the aortic graft to be perfectly intact. This case was the only one in the series with another associated cardiac defect, namely, rheumatic mitral insufficiency and stenosis. The other 9 in this series are doing well since the operation.

Pre-operative medication consisted of 0·6 mg. of atropine and either 0·16 mg. of morphine or 200 mg. of nembutal. Induction of anæsthesia was begun with either pentothal or nitrous oxide. This was then followed and maintained throughout the operation with endotracheal ether, with circle absorption technique.

Electrocardiograms were taken both before and during the operation, in the first two cases practically continuously during the surgical procedure. In the subsequent cases, long strip tracings were taken during important phases of the operation; namely, induction of anæsthesia, mediastinal exploration and dissection of the aorta, clamping of the aorta, release of the aortic clamps after primary anastomosis or vascular grafting, and closure of the chest.

The electrocardiograms were all recorded by means of the direct-writing Sanborn Viso-Cardiette. The pre-operative electrocardiograms included the three standard bipolar limb leads, the three augmented unipolar limb leads, and six unipolar chest leads (V1–V6). During the operation, records with the three standard limb leads were taken whenever possible or at least long strips of one bipolar limb lead.

Results

The electrocardiographic features observed in these 10 cases, both before and during the operation, are summarized in Table I. More detailed analyses are presented in Table II. While Cases 2 and 7 had pre-operative electrocardiograms within normal limits, the remaining 8 shown were abnormal. Seven showed left ventricular hypertrophy as is often observed in this condition.

TABLE I

ELECTROCARDIOGRAPHIC FEATURES

	No. of Cases
Before operation:	
1. Within normal limits	2
2. Left ventricular hypertrophy	7
3. Sinus arrhythmia with nodal escapes	1
4. Prolonged A–V conduction	1
5. Incomplete bundle branch block	2
6. S–T depression	2
During operation:	
1. Tachycardia (including nodal tachycardia, 2)	10
2. Ectopic ventricular beats	1
3. P–R prolongation (in 1 before operation also)	2
4. QRS abnormalities: lowering of voltage (3), slurring or aberration (1), and QRS prolongation, as pre-operatively (2)	6
5. S–T depression	4
6. T wave changes: lowering of voltage (4), inversion (2), and widening (1)	7

Normal sinus rhythm was present in all, except for Case 5, which showed a rather slow sinus arrhythmia with occasional nodal escapes. Cases 9 and 10 had a QRS duration longer than 0·10 but not beyond 0·12 sec., which was interpreted as incomplete bundle branch block (Burch *et al.*, 1949). In addition, Case 9 also had a P–R interval of 0·21 sec., against the expected normal of 0·19 sec. for her age and heart rate. The S–T segment depressions noted in Cases 4 and 10 were not more than 0·5 mm. below the base-line.

In Table II, it is evident that some change in the electrocardiogram developed in all instances. The most uniform feature was the increase in heart rate which occurred during the induction of anæsthesia and persisted throughout the operation. In 8 cases this was an ordinary sinus tachycardia; in 2, however, the pacemaker shifted from the sinus node to the A–V node during the operation, with the nodal rhythm at a faster rate than the preceding sinus rhythm. No other arrhythmia was noted except for ectopic ventricular beats in Case 6.

Two instances of prolonged A–V conduction were observed. In Case 5, the P–R interval lengthened from a normal of 0·16 to 0·19 sec., at the moment of opening the chest. It remained so until the closure of the chest, when it came down to 0·18 sec., the upper limit of normal for the heart rate and age of the patient. In Case 9, the P–R interval was 0·21 sec. at the start of the operation with a heart rate of 84 a minute, and as it became 0·22 sec. during the clamping of the aorta when the heart rate increased to 105 there was some functional lengthening. Under normal circumstances, the P–R interval should shorten as the heart rate increases.

On the other hand, the two cases with pre-operative prolongation of the QRS interval continued to show this abnormality throughout the operation, although their heart rates became faster.

Lowering, slurring, or aberration of the QRS complexes, as a rule, was never marked. It developed usually during the early part of the operation and was probably related to positional shift of the heart, especially when lowering of the QRS occurred only in one lead. In some instances, however, the QRS changes were accompanied by S–T and T wave abnormalities. These changes seemed to start during the opening of the chest but tended to become more evident during the clamping of the aorta and at times even earlier, that is, during mediastinal exploration and dissection of the aorta. In Case 4, the S–T depression reached as much as 2 mm. below the base-line, and in Case 10 the T III became as deeply inverted as 5 mm. Similarly, in Case 6, the occasional ectopic ventricular beats occurred slightly more frequently during the aortic clamping than at any other phase of the operation.

During the release of the clamps and subsequently during the closure of the chest, the electrocardiogram generally started to show evidence of improvement. This consisted either in increase of QRS voltage, diminution or disappearance of S–T depression, or improvement of the T waves. Again, in Case 6, the ectopic ventricular beats became less frequent until they disappeared completely. In Case 5, however, T I continued to be less upright than before operation; actually it had been gradually dropping in voltage since the start of the operation.

TABLE II

ELECTROCARDIOGRAPHIC FINDINGS DURING OPERATION

Case No. Sex and Age	Induction of Anesthesia	Opening of Chest	Dissection of Aorta	Clamps on Aorta	Clamps off Aorta	During closure of Chest
1. M. 25 yrs.	S. tachycardia: 125 Slight depression of S–T2, 3 Diphasic T2 Negative T3	—	S. tachycardia rate, 136 More depression of S–T2, 3 to 1 mm.	Rate, 110	Less depression of S–T2, 3	—
2. M. 10 yr.	Sinus tachycardia rate, 136 Lowered T1	Lowered QRS. voltage	—	Rate, 160 Isoelectric P Widened T2 to 0·18 sec.	Increased QRS voltage	Pre-op. QRS volt. T1 still low Depressed S–T in 2 and 3
3. M. 17 yr.	Nodal tachycardia 115 Flat to negative P waves	Sinus rhythm rate, 100 Upright P's; P–R: 0·14	Nodal tachycardia Rate, 125	—	—	—
4. F. 11 yr.	S. tachycardia: 115 Low T1 (0·75 mm.) Depressed S–T Negative T3	Rate, 167 Lowered QRS1 Diphasic T1	—	Rate, 150 More depression of S–T2 to 2 mm.	—	—
5. M. 20 yr.	S. tachycardia: 110 P–R, 0·16 T1, 1·5 mm.	P–R, 0·19 Lower T1 (1 mm.)	—	—	Further lowering of T1 (0·5 mm.)	P–R, 0·18
6. M. 14 yr.	S. tachycardia rate, 115	—	Rate, 125 Ectopic V. B.	Rate, 150 More ectopic V. B.	Rate, 136 Few ectopic V. B.	—
F. 35 yr.	Rate, 105 T1, 0·75 mm.	Rate, 115	Slurred QRS	—	—	—
8. M. 12 yr.	S. tachycardia rate, 125	—	Rate, 135 Negative T3	—	—	—
8. F. 23 yr.	Rate, 84 P–R, 0·21 QRS, 0·12	S. tachy., 115 Depressed S–T1 Lowered QRS	—	Rate, 105 P–R: 0·22	—	Increased QRS voltage
10. M. 18 yr.	Nodal tachycardia rate, 150 Deep neg. T2, 3 Depressed S–T2, 3	Negative T3 to 9 mm P–R, 0·12 PS. tachycardia	—	P–R, 0·14 Sinus rhythm Negative T3 to 5 mm.	Negative T3 to 3mm.	P–R, 0·14 Negative T2 to 3 mm.

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Discussion

The sinus tachycardia that occurred in our cases presumably was an effect of the anæsthetic agent used—ether. Thus, this increase in heart rate developed before the opening of the chest and persisted throughout the entire procedure. In the two cases with nodal rhythm (Fig. 1), the fact

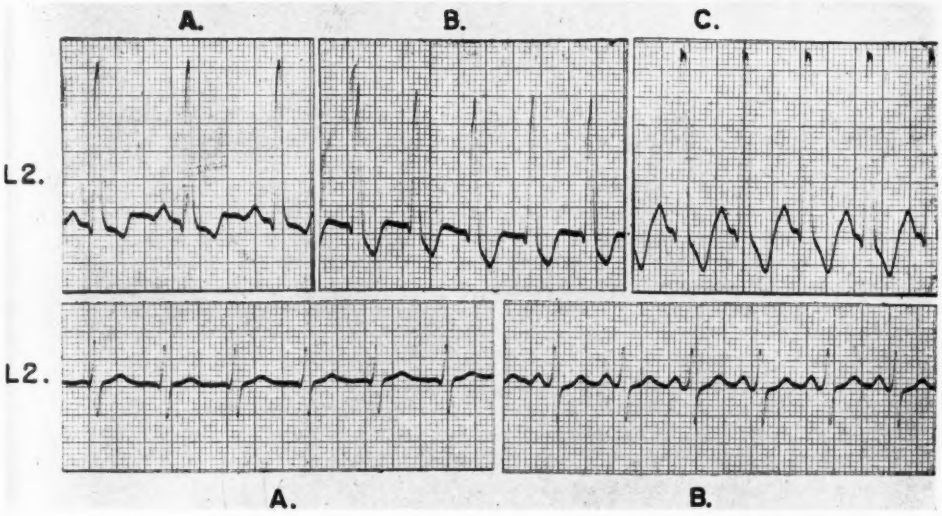

Fig. 1.

Upper curves. Case 10, lead 2. (A) Normal sinus rhythm before operation; (B) nodal tachycardia, during induction of anæsthesia; and (C) sinus tachycardia, during opening of the chest and the rest of the operation.
Lower curves. Case 3, lead 2. (A) Nodal rhythm during induction of anæsthesia; and (B) sinus rhythm, during opening of the chest. After the latter, nodal rhythm again developed and persisted throughout the rest of the operation. Sinus rate pre-operatively was 82 a minute.

that the ventricular rate then was faster than when it was under normal sinus control indicates that there was more than a simple depression of the sinus node. Under ordinary circumstances, nodal rhythm should have a slower rate than the sinus rhythm. It seems logical to consider, as Ziegler (1948) observed in his series, that an A–V nodal rhythm with a faster ventricular response than during the preceding normal sinus rhythm, is a true active ectopic nodal tachycardia. In 129 instances of A–V nodal rhythm, Ziegler found 33 (25%) in which this active ectopic nodal tachycardia occurred. As in his cases, our own would suggest an interplay of several factors. Depression of the S–A node was probably mediated through the vagus, both by the morphine administered pre-operatively and by incidental vagal stimulation during the mediastinal dissection. On the other hand, the heightened irritability of the lower pacemaker, the A–V node in our cases, may be due partly to the morphine itself but more probably to ether. This is also true with the occurrence of ectopic ventricular beats in Case 6 (Fig. 2A). It is of interest, however, that none of these disturbances was severe in any of our cases. The tachycardia, sinus or nodal, never rose to unusual rates, and the ectopic ventricular beats were never multifocal nor unusually frequent. That no serious arrhythmia developed is somewhat against the frequency of its occurrence reported in studies by other authors done during intrathoracic surgery (Feil *et al.*, 1939, and Currens *et al.*, 1943). It is felt that this may be due to their use of cyclopropane (Kurtz *et al.*, 1936, Taylor, 1941, and Theines, *et al.*, 1941), which is known to increase the irritability of the myocardium.

Another evidence of vagal influence is the prolongation of A–V conduction that occurred in

2 cases (Fig. 2B and 3). While Ziegler observed only one instance of P–R prolongation, Burstein *et al.* (1949) and Gullickson and Campbell (1949) noted the development of this delayed A–V conduction during vagotomy and during vagus nerve stimulation incidental to pulmonary hilar traction and bronchial manipulation.

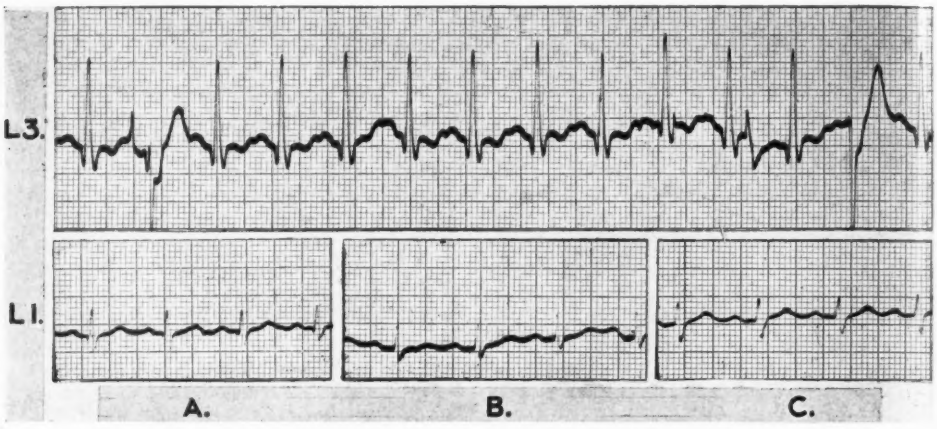

FIG. 2.

Upper curves. Case 6, lead 3. Ectopic ventricular beats and sinus tachycardia, both of which were more frequent at the time of clamping of the aorta as shown here.

Lower curves. Case 5, lead 1. Slight P–R changes during the operation. (A) P–R of 0·16 sec., pre-operatively and during induction of anæsthesia; (B) P–R of 0·19–0·20 sec. during opening of the chest; (C) P–R of 0·18 sec. during closure of the chest.

The QRS lowering, slurring, or aberration was never severe in degree and was probably caused by changes in heart position during the operation. However, when associated with S–T and/or T wave changes (Fig. 3 and 4), they were probably on the basis of myocardial hypoxia. Thus, they tended to be greatest when the chest was opened and the lung collapsed. The improvement of these changes towards the end of the operation and during the closure of the chest gives further support to this.

As a whole, therefore, no alarming electrocardiographic abnormalities occurred even during the critical phases of the operation pointed out earlier in this paper. There is, however, some indication from Table II that the changes noted here occurred or were apt to be more marked during the clamping of the aorta and at times slightly earlier, that is, during mediastinal exploration and dissection of the aorta prior to its clamping. This tendency involved essentially all the changes observed in these 10 cases. It is probable then that the underlying mechanism is an interplay of vagal influence and myocardial hypoxia.

From earlier experiences it was believed desirable, if possible, to reduce the blood pressure to approximately 140 or 150 mm. Hg. systolic before clamping of the aorta. The measures taken were pre-operative sedation with morphine, and delaying the replacement of blood during the early phases of the operation. In our cases the average blood pressure immediately prior to clamping was 141/94 mm. In all instances this pre-clamping level was much lower than that before operation. The average blood pressure on admission was 175/99 mm. In Case 10, it came down from 200/80 on admission to 120/90 mm. at the time of the clamping.

After placing of the aortic clamps, the average blood pressure was 165/107 mm., which meant an average rise of 24 mm. systolic and 13 mm. diastolic over the pre-clamping level. The highest individual rise was in Case 1, where the pre-clamping level of 150/104 rose to 214/154 during the

clamping; this unusual rise was probably related to the clamping of the subclavian artery which was necessary in this case during the aortic resection and anastomosis. In Case 8, there was no significant rise during the clamping, the blood pressure remaining at about 140/100 mm.

It is clear that cardiac disturbances are an actual potential danger, as suggested by the observation here noted; namely, the tendency of all electrocardiographic abnormalities to occur or to be more

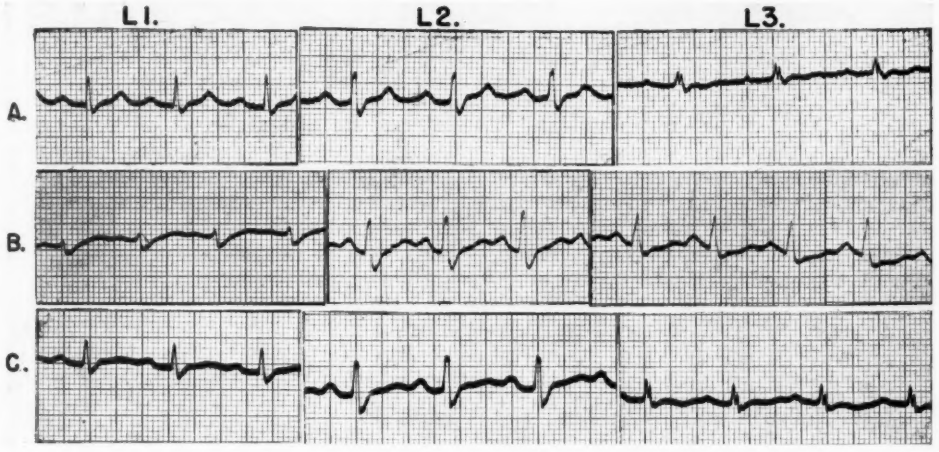

FIG. 3.—Case 9, leads 1, 2 and 3. (A) Pre-operatively and during earlier phases of operation: P–R of 0·20–0·21 sec. and QRS of 0·12 sec. (B) During clamping of the aorta: faster rate, lowering of QRS1 and T waves, S–T depression, P–R of 0·22 sec. and QRS of 0·12 sec. (C) During chest closure and end of operation: increase in QRS voltage and T waves in lead 1, with the same P–R and QRS intervals.

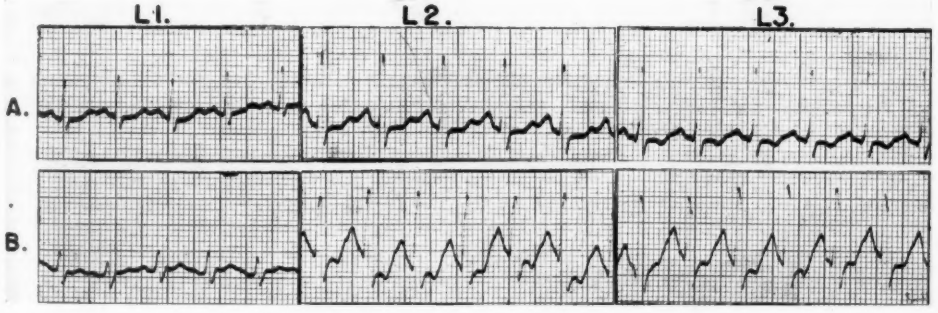

FIG. 4.—Case 4, leads 1, 2, and 3. (A) Pre-operatively and during induction of anæsthesia: some S–T depression more marked in lead 2, and negative T in lead 3. (B) During clamping of the aorta: more rapid rate, lowered QRS in lead 1, lowered to diphasic or negative T waves, and S–T depression.

marked during this phase of the operation. This confirms the impression formed in some of the earlier cases of the existence of such a danger. While no direct proof can be provided, it seems probable that the absence of serious cardiac disturbances may have been in some measure due to the precautions previously mentioned to prevent excessive rise of blood pressure following the clamping of the aorta.

In contrast, during and following the release of the aortic clamps, not only was there no further

electrocardiographic abnormality noted but instead signs of improvement already started to appear. This was indicated by the improvement of the QRS voltage and configuration as well as of the S–T and T wave abnormalities that may have occurred earlier (Fig. 3). That this should occur is to be expected as the factors producing myocardial hypoxia are removed and as a return of the cardiodynamics towards normal is started. This also confirms the importance of a gradual release of the aortic clamps. Complications were noted in the past at this stage of the operation in cases where the aortic clamps were released suddenly or rapidly. In our cases, the average blood pressure after removal of the aortic clamps was 115/75 mm. The maximum drop was 90 mm. systolic and 50 mm. diastolic from the highest rise reached during the clamping. The lowest individual level was 100/80 and the highest was 140/100 mm. In no instance did the blood pressure drop to shock levels.

Finally, the continued improvement of the electrocardiogram up to the completion of the operation offers evidence of the expected return of the circulation towards normal following the removal of the aortic block.

One other interesting observation from this study is the fact that P–R or QRS prolongation, unless of severe degrees, is not an absolute contraindication to this operation nor do they constitute an unusually serious risk. In fact, there may be some transient lengthening of the P–R interval during the operation, presumably on the basis of vagal influence. On the other hand, the two cases with slight prolongation of the QRS interval maintained this (Fig. 3) throughout the operation, which suggests that the operation does not aggravate this abnormality. This is confirmed by a recent case of Littman and Warren (personal communication), a patient who had complete left bundle branch block with the same QRS duration of 0·14 sec. before and after the operation. These observations, though limited, are of practical interest inasmuch as some of the unsuccessful cases in the past had been attributed to pre-existing P–R and/or QRS prolongation. They also suggest that for the evaluation of the surgical risk the state of myocardial function is a more critical basis than are minor disturbances in conduction or rhythm.

Summary and Conclusions

Ten cases of coarctation of the aorta were studied from the point of view of electrocardiographic changes during the operation. The surgical procedure was resection of the coarctation followed by either end-to-end anastomosis or else insertion of an aortic graft. Ether was the anæsthetic agent used in all cases.

Several abnormalities were noted in the electrocardiograms before operation. They were chiefly evidences of left ventricular hypertrophy, and in a few instances also mild P–R or QRS prolongation.

The electrocardiographic abnormalities further observed during the operation, either in cardiac rhythm, conduction or ventricular activity, are tabulated and discussed. None of these was considered serious. The changes tended to occur or to be more marked towards and during the clamping of the aorta. No further abnormality was noted either during the release of the aortic clamps or immediately after the operation. Instead, the electrocardiogram started to show signs of improvement from the time the aortic clamps were released.

The two cases who had or developed P–R prolongation as well as those with slight QRS prolongation suggest that such conduction defects, unless severe, are not absolute contraindications to the operation.

The authors are indebted to Dr. Robert E. Gross for making this study possible.

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SPLENIC ENLARGEMENT IN CONGESTIVE HEART FAILURE AND ACTIVE RHEUMATIC INFECTION

BY

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It is generally stated that the spleen rarely if ever enlarges sufficiently to become palpable in uncomplicated congestive heart failure. Rolleston (1908) and Held (1919) both concluded that a palpable spleen in congestive failure was due to some complication. Talley and Lindsey (1924) in 198 cases of congestive failure in adults found 3 with palpable spleens. Fishberg (1940) in discussing the question concludes that the spleen may enlarge at the onset of failure, but that, later, it decreases in size owing to fibrosis and to contraction, which contributes to increasing the circulating blood volume, so that in chronic failure a condition of " cyanotic atrophy " of the spleen is found. Fishberg mentions the following causes of a palpable spleen in heart failure:—

(1) Active infection, e.g. rheumatic carditis.
(2) Cardiac cirrhosis of the liver from chronic right-sided heart failure.
(3) Mediastino-pericarditis.
(4) Large left pleural effusion displacing the spleen downwards.

Similar views have been expressed by Boyd (1940) and Ravenna (1943). Fowler (1947) from a study of the pathological records at the Peter Bent Brigham Hospital, Boston, concluded that 12 out of 97 cases of uncomplicated congestive failure had spleens large enough to be palpable, assuming that a weight of 300 g. or more would render the spleen palpable as suggested by Barron and Litman (1932). In only one of these twelve cases was the spleen actually recorded as being clinically palpable, and this discrepancy was attributed to special difficulty in palpation of the spleen in cardiac cases—for example—ascites, œdema of the abdominal wall, and lack of co-operation on the part of the patient. In failure due to rheumatic valvular disease, the spleen was always large enough to be palpable, and cardiac hepatic cirrhosis was common. Wahi and Mathur (1949) found, in 690 cases of congestive failure studied in India, 7 per cent with palpable spleens. They also noticed from pathological observation that a spleen weighing 300 g. or more was often found although it had not been palpated clinically.

Present Investigation

During the last two years, the occurrence of clinical splenic enlargement has been investigated in 206 cases of congestive heart failure and in 67 cases of active rheumatic carditis without failure. The selection of cases was difficult on account of the frequency of splenic enlargement in Egypt from bilharziasis and malaria, but as far as possible all such cases, including doubtful ones, were excluded. Cases with bacterial endocarditis were also excluded.

The cases studied were grouped as follows:—

I (*a*) Congestive failure due to rheumatic heart disease—111 cases.
(*b*) With active rheumatic infection—14 cases.
(*c*) Without active infection—97 cases.
II Congestive failure of non-rheumatic ætiology—95 cases.
III Active rheumatic infection without congestive failure—67 cases.

In these 273 cases, a palpable spleen was found in 7 in which no other cause than failure or active rheumatic infection existed. Of these 7 cases of splenomegaly, 3 had failure and active rheumatic infection; 2 had failure due to chronic rheumatic heart disease, and 2 had active rheumatic infection without failure. No case of enlarged spleen occurred in the group of 95 cases of failure of non-rheumatic ætiology.

Summary of Cases

I (*a*) *Congestive failure with active rheumatic infection.*

Case 1. Male, aged 17, had recurrent rheumatic infection with failure. Heart enlarged with signs of mitral stenosis and congestion of predominantly hepatic type with little œdema. Liver enlarged five fingers below costal margin in mid-clavicular line, and pulsating. Right hydrothorax. Fever, joint pains, rheumatic nodules and raised E.S.R. The spleen was sometimes palpable at the costal margin, sometimes impalpable.

Case 2. Male, aged 14, with cardiac symptoms of two years' duration. Signs of old mitral disease with an acute exacerbation of rheumatic carditis, and congestion of hepatic type. The spleen was palpable three fingers below the costal margin, soft and tender. Fatal termination; no necropsy obtained.

Case 3. Female, aged 30, with chronic mitral disease. Admitted to hospital with acute rheumatic fever and active carditis, with slight congestion of neck veins and liver. Dry pericarditis, right pleural effusion, and consolidation at the left base developed, venous engorgement increased, and œdema appeared. The spleen, not palpable on admission, was felt three fingers below the costal margin, soft and tender. Bilateral pleural effusions needed paracentesis, and joint pains with irregular fever persisted. With subsidence of active infection and failure, first the spleen, then the liver diminished in size, and two months after admission, when failure had subsided, the spleen was no longer palpable.

I (*b*) *Congestive failure due to rheumatic heart disease without active infection.*

Case 4. Male, aged 19, with history of urinary bilharziasis 8 years previously, and of cardiac symptoms of two years' duration. Heart enlarged with signs of mitral stenosis and congestive failure with tricuspid regurgitation, but no œdema. Liver pulsating and enlarged three fingers below costal margin, firm and tender. Spleen palpable three fingers below costal margin, firm but not tender. As the dregree of congestion waxed and waned, the size of the spleen varied accordingly. Two months later, when quite free from failure, the liver enlargement persisted, and the spleen was just palpable in the right lateral position.

Case 5. Male, aged 17, with history of urinary bilharziasis 7 years previously. Signs of mitral disease with aortic regurgitation, and congestive failure. Liver enlarged and pulsating, five fingers below costal margin, and tender. A palpable rub over liver due to perhepatitis developed. As the patient improved slightly, the spleen became smaller and less tender, remaining just palpable, but the liver was unchanged.

Case 6. Male, aged 15, with history of periodic fever, arthritis, sore throat, epistaxis, and chorea during the last 3 years. Rheumatic nodules, raised E.S.R., and slight fever. Signs of mitral stenosis without heart failure. Spleen enlarged one finger below costal margin, soft and tender.

Case 7. Female, aged 25, admitted to hospital with subacute rheumatic polyarthritis, rheumatic nodules, and raised E.S.R. During 6 weeks in hospital, the spleen was palpable one finger below costal margin, soft and tender, and the arthritis lingered.

Discussion

It is evident that palpable splenic enlargement is rare in congestive heart failure, for it occurred in only 5 of our 206 cases, and no instance of it occurred in cases of failure of non-rheumatic ætiology. When splenomegaly does occur, there is some special cause, and the following factors appeared to favour it:—

(1) congestive failure with predominantly hepatic congestion,
(2) associated liver cirrhosis, and
(3) active rheumatic infection.

In the rheumatic group, splenic enlargement occurred in cases of mitral stenosis with congestion of predominantly hepatic type, though not all such cases presented splenomegaly. In 3 cases of this type, 2 were associated with active rheumatic infection, and 1 with liver cirrhosis. Cases 4 and 5 had an associated liver cirrhosis, probably of bilharzial origin, and one of these had perihepatitis; in both liver enlargement persisted after failure had subsided. It may be assumed that liver cirrhosis increases the splenic congestion due to heart failure.

Active rheumatic infection by itself rarely accounts for a palpable spleen (3 per cent of our cases), but when associated with heart failure splenomegaly is more frequent (20 per cent of our cases). In 3 cases with splenomegaly and active rheumatic infection, rheumatic nodules were present, indicating a severe infection.

The size of the spleen varied from being just palpable to three fingers below the costal margin. It was usually soft and tender except in two cases with liver cirrhosis In 3 cases the size of the spleen fluctuated with the degree of failure and rheumatic activity.

Summary

Previous reports relating to palpable splenomegaly in congestive heart failure and active rheumatic infection are reviewed.

A series of 206 cases of congestive heart failure and 67 cases of active rheumatic infection without failure has been investigated in regard to the occurrence of palpable splenic enlargement. This occurred in 7 cases; 5 with congestive failure and 2 with active rheumatic infection without failure.

The factors responsible for splenic enlargement are discussed.

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PRODROMAL SYMPTOMS IN MYOCARDIAL INFARCTION

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Sampson and Eliaser in an article entitled " The Diagnosis of Impending Acute Coronary Arterial Occlusion " in 1937 described 29 cases " exhibiting attacks of præcordial pain of prolonged duration which," they considered, " might represent a precursor phenomenon of characteristic acute coronary arterial occlusion." Feil, in the same year, described fifteen more cases of this syndrome, which he named " preliminary pain in coronary thrombosis." Brill in 1938, in a review of earlier clinical reports on the subject, points out that, although the concept appeared new, it had already received mention by earlier authors and quotes Herrick (1912), Parkinson and Bedford (1928), Levine (1929), Willius (1936), and Conner and Holt (1930), who mention the occurrence of transitory chest pain before myocardial infarction of a nature different from previous anginal attacks. More recently, Langston (1939) has described a small series and Yater (1948) a large series of 60 cases in a review of coronary artery disease in men under the age of forty. It is interesting to note that, among earlier authors, Caleb Parry in 1799, described a case which, in the light of present knowledge, almost certainly belonged to this group.

General Considerations

The subject of prodromal symptoms in myocardial infarction is a difficult one, since it lies in the ill-defined borderline state between the clinical syndrome of angina of effort and the pathological state of myocardial infarction which has been referred to by Blumgart *et al.* (1940) as " coronary failure." In this state, angina pectoris of many different types may be met, almost protean in its minor variations, yet constant in its major essentials, and from this state the patient may return to normal health, may proceed to or continue a long history of angina of effort, or may go on to myocardial infarction. The relative incidence of these three modes of termination is not obtainable in a hospital series, since few of those who do not suffer infarction are referred to hospital. Hospital records, however, provide good facilities for estimation of the relative frequency of such anginal prodromal symptoms in myocardial infarction and such a survey is attempted in this paper.

It is suggested that prodromal symptoms occur sufficiently frequently in myocardial infarction to make a recognizable clinical group. If this assumption is correct, its potential importance in the prophylactic treatment of myocardial infarction in such cases with rest and possible anti-coagulant therapy is important, as suggested by Wood (1949).

Incidence of Prodromal Symptoms in Myocardial Infarction

In an attempt to assess the relative frequency of prodromal symptoms in myocardial infarction, it was necessary to include in the series only those cases of myocardial infarction that allowed a clear decision to be made as to whether or not these were present and in which evidence of myocardial infarction was definite. Criteria for inclusion in the series were as follows.

1. Post-mortem evidence or good electrocardiographic evidence that myocardial infarction had occurred. (In the earlier years, standard and CR leads alone were used; later the unipolar præcordial and limb leads were added.)

2. Clear clinical evidence of the exact time of the occurrence of infarction (except where serial electrocardiograms fixed the time accurately).

3. A good history of the events preceding infarction.

4. In the " prodromal " group, a history of anginal pain usually with atypical features or intensification or change in character of previous angina, preceding myocardial infarction by not more than three months.

Cases not fulfilling these criteria were rejected.

In a series of 139 cases of myocardial infarction acceptable by the above criteria, who were admitted to Hammersmith Hospital over a period of fourteen years, 40 showed prodromal symptoms, giving an incidence of 29 per cent.

Comparison of Ætiological Factors and Prognosis in the Groups with and without Prodromal Symptoms

General factors. No significant differences were found in the age distribution, sex incidence or the incidence of hypertension in the prodromal group and the group without prodromal symptoms. The criteria for the diagnosis of hypertension were a systolic pressure of 150 or higher, or a diastolic pressure of 90 or higher. There was no significant difference in the incidence of diabetes mellitus in the two groups.

Previous history of typical angina of effort. In this series, 21 per cent of the prodromal group had a previous history of typical angina of effort as against 32 per cent in the group without prodromal symptoms. The border-line between angina of effort and the atypical pain of prodromal symptoms was often difficult to distinguish. There was a small group of patients with progressive angina pectoris in which the severity and frequency of attacks increased gradually over a period of years, finally culminating in myocardial infarction. These cases with a long progressive history (over 3 months) were excluded here from the prodromal group.

Angina of effort following myocardial infarction preceded by prodromal symptoms. Of the prodromal group, who survived the first myocardial infarction and were followed up, 79 per cent developed angina of effort, as compared with a figure of 59 per cent in the group without prodromal symptoms. There was, however, no significant difference in incidence if, from the latter group, a small sub-group of 14 cases who had no pain either at the time of myocardial infarction or afterwards be excluded. The angina following myocardial infarction is often atypical, lasting longer than usual and sometimes coming on at rest. For that reason it was difficult to obtain a clear history of prodromal symptoms preceding a second or a third myocardial infarction in patients with such angina, and only one case is included in this series. Of those who did not develop angina after a first myocardial infarction, none had prodromal symptoms before the second infarction.

Fatality rate. In the prodromal group, 39 cases had prodromal symptoms preceding their first attack of myocardial infarction and of these 5 terminated fatally, giving a fatality rate of 13 per cent. Of four cases in this group who had a second myocardial infarction, only one had clearly recognizable prodromal symptoms and this patient died. The overall fatality rate, without taking into account previous or subsequent attacks of myocardial infarction, was 15 per cent. In the group without prodromal symptoms, 30 patients died after a first attack of myocardial infarction giving a fatality rate of 30 per cent; 17 died out of 26 who had a second attack, and three out of three died who had a third attack. The overall fatality rate, without taking into account previous or subsequent attacks of myocardial infarction was 50 per cent. The fatality rate in the two groups is, however, not strictly comparable, since, following the introduction of anticoagulant therapy, a greater number of cases in the prodromal group received treatment than in the other group.

Prodromal Symptomatology

Total duration. The shortest time between the onset of pain and the occurrence of myocardial infarction was three days, the longest by arbitrary definition twelve weeks. In thirteen cases prodromal symptoms occupied less than one week; in seven cases less than two weeks; in six cases less than three weeks; in eleven between three and eight weeks; and in three cases three months. The average duration of prodromal symptoms was three and a half weeks.

Character of the pain. The onset of the pain was usually described as being sudden, but on careful questioning patients would often admit to vague substernal discomfort of the same type some weeks earlier. The pain was typical anginal pain in site and radiation, being sternal or præcordial, radiating in some cases to the arms, shoulders, neck, jaws, or epigastrium. In character it was most often constricting, sometimes a dull ache.

Duration of individual attacks. This varied between five minutes and six hours. In fourteen cases, attacks never exceeded five minutes; in eight cases, fifteen minutes. In eight cases, they lasted up to thirty minutes; in one case up to one hour; in five cases, up to three hours; in one, up to six hours. In one case the pain was continuous for three weeks. In two cases, the duration of attacks was not recorded.

Precipitating factors. In eighteen cases, pain came on only with effort and never at rest. In four cases, pain came on at rest and was never related to effort; in one of these cases, there was definite association with worry; in another, the symptoms were unusual in that the pain was continuous for three weeks. In eighteen cases, attacks came on both on effort and at rest, out of which eleven had their first attack on effort, and six at rest, while in one the circumstances accompanying the first attack were unrecorded. There appeared to be no relationship between the varying lengths of attacks of pain and their precipitating factors. Emotion, meals, and temperature changes were less frequent precipitating factors, each occurring in only four to five cases in the group.

Relieving factors. Rest relieved the pain in all cases except seven, but in some this effect was not constant. Amyl nitrite relieved the pain in nine cases but did not relieve in one; in the remainder it was not tried or case records were inadequate.

Associated dyspnœa or congestive heart failure. Twenty cases suffered dyspnœa associated with the prodromal anginal pain. Thirteen of these had associated hypertension; the remaining seven had no evidence of respiratory disease or of cardiovalvular disease other than the myocardial infarction. Two cases finally presented with congestive cardiac failure at the time of myocardial infarction; both were hypertensive.

Periodicity of pain. The periodicity of pain varied greatly. In some cases it was six times a day; in others, once a week.

General trend. A crescendo quality was observed in 29 cases. This was seen in increased severity of pain in 20 cases; in increased frequency of attacks in 17; in diminished effort-threshold in 14 (i.e. less and less work was required to bring on the pain); in increased duration of attacks in 13. The remaining 11 cases showed no crescendo quality.

Analysis of the quality of prodromal pain in the present series showed that in all cases the pain possessed features that were atypical of classical angina of effort although the combination of these features varied from case to case. The most frequent finding was a crescendo nature in the symptoms during the short period of prodromal pain, which was seen in 29 out of 40 cases. The second distinguishing feature was the prolonged nature of the attacks. The third feature was the inconstant relation of the pain to effort: there was a group in which the pain was induced by effort, another in which the pain occurred at rest, and a third in which both occurred.

Electrocardiograms during the Prodromal Period

Electrocardiograms were obtained in ten cases during the prodromal period and were divisible into three main groups, those without clear evidence of myocardial ischæmia, those with evidence of ischæmia after exercise, and those with evidence of ischæmia at rest. There were four cases in

the group without evidence of myocardial ischæmia. Three of these were hypertensive and had graphs that showed left ventricular preponderance (Fig. 1). The fourth case showed a right bundle branch block picture in the electrocardiogram (Fig. 2) which may have been evidence of myocardial ischæmia in this case. None of these cases were subjected to an exercise test.

Of the two cases showing an ischæmic type of graph on exercise, both showed S–T depression in leads V3 and V5 (Fig. 3), a pattern which is ascribed by Wilson (1947) to transient endocardial ischæmia.

The third group, which showed evidence of myocardial ischæmia at rest, consisted of four cases. The feature common to all four was the presence of S–T segment elevation and T wave inversion in the unipolar chest leads, without pathological Q waves (Fig. 4, 5, and 6).

Bayley (1943) pointed out that the pattern of deep symmetrical T wave inversion might or might not be followed by myocardial infarction and stated that it was caused by " acute local ventricular ischæmia " without infarction.

Clinical, Electrocardiographic and Post-mortem Evidence of the Occurrence of Myocardial Infarction in the Prodromal Group

In thirty-nine patients there was a clear-cut history of pain, worse than any previously experienced, which represented the summit of the crescendo of symptoms and was considered to mark the time of the occurrence of myocardial infarction. In twenty-three cases, the attack came on at rest, and in fifteen it occurred in bed. In fifteen cases, the pain came on whilst carrying out normal daily occupations. The duration of pain was usually prolonged; in fourteen cases more than twenty-four hours; in eight cases about twelve hours; in six cases, eight hours; in six cases, three hours; in three cases, one hour; in one case it was continuous with prodromal pain, and in one the time was unrecorded. In ten cases, the attack was associated with vomiting. In the remaining single case, not experiencing a major attack of pain at the time of myocardial infarction, the patient suffered repeated short anginal attacks at rest and finally showed signs of early congestive cardiac failure.

Electrocardiograms after the occurrence of myocardial infarction were obtained in all cases. In thirty cases, standard and unipolar limb and chest leads were taken. Here the diagnostic criteria were pathological Q waves with typical S–T segment and T wave changes. In ten cases electrocardiographic evidence of myocardial infarction, although definite, was less complete. In three, the standard and CR1, CR3, and CR4 leads were taken; in four the standard and CR4 leads; in three the standard leads alone. Evidence of infarction in this sub-group lay in Pardee coving with a sharply inverted T wave; in addition, six cases showed pathological Q waves.

Four cases came to post-mortem examination, and in these the clinical diagnosis of myocardial infarction was confirmed.

Pathology of Prodromal Symptoms

In this series, evidence as to the pathogenesis of prodromal symptoms has been obtained from post-mortem data in four cases. One case was of special interest pathologically and is therefore reported in full here.

Case A. K. A hypertensive male, aged 53, a tailor's presser, who had previously been in good health, had a sudden attack of severe sub-sternal gripping pain on exertion. The pain lasted two to three minutes and disappeared on resting. During the next week he was symptom-free, except for slight dyspnœa on exertion. At the end of this time he had recurrences of angina of effort, at first once a day, later three or four times a day, which gradually became more severe. Finally, after a further week, he had a severe attack of pain at rest lasting twenty minutes, followed by three to four similar attacks at rest in the next twelve hours.

He was admitted to hospital with a provisional diagnosis of myocardial infarction and an electrocardiogram two days later (Fig. 4) showed an ischæmic pattern with deep symmetrical T wave inversion in all chest leads. There were no significant blood pressure changes during the

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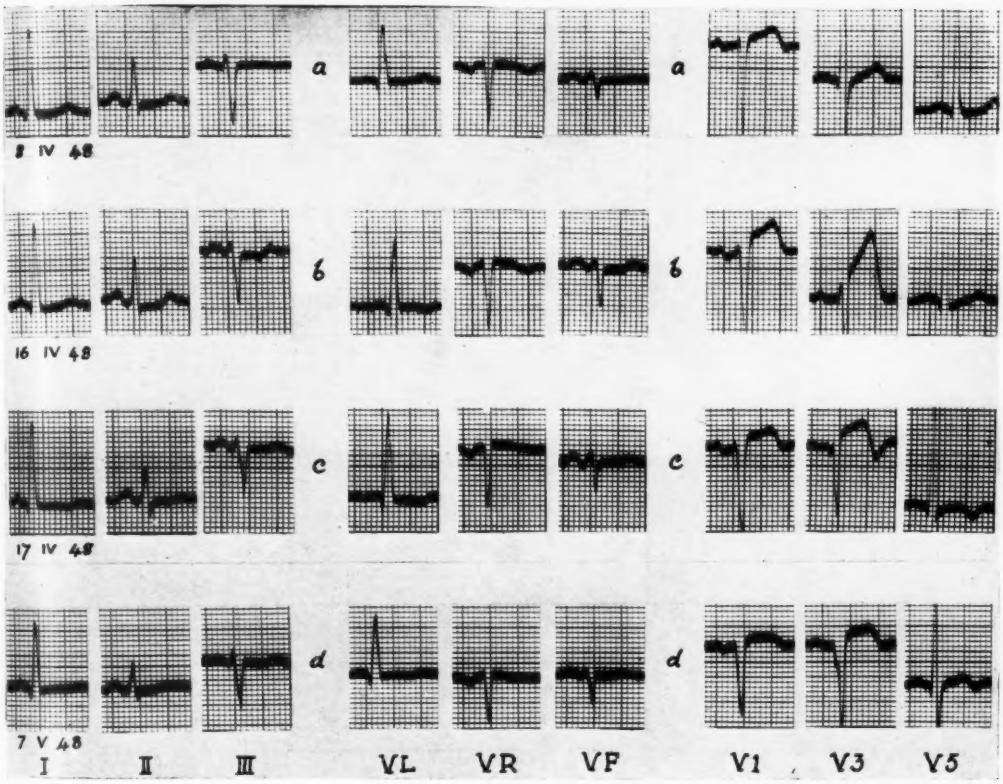

FIG. 1.—Case with no definite evidence of myocardial ischæmia during the prodromal period. Exercise test not performed. (a) EC during prodromal period; left ventricular preponderance; (b), (c), (d) progressive changes of acute anterior myocardial infarction.

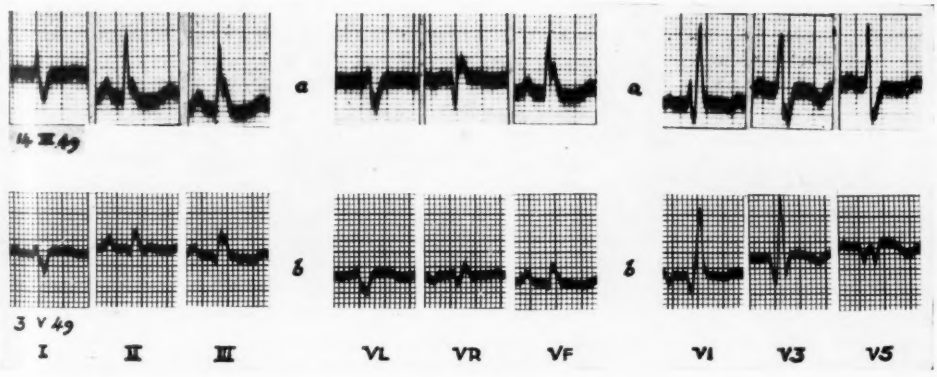

FIG. 2.—Case with no definite evidence of myocardial ischæmia during prodromal period. Exercise test not performed. (a) EC during prodromal period; R.B.B.Bl.; (b) acute anterior myocardial infarction.

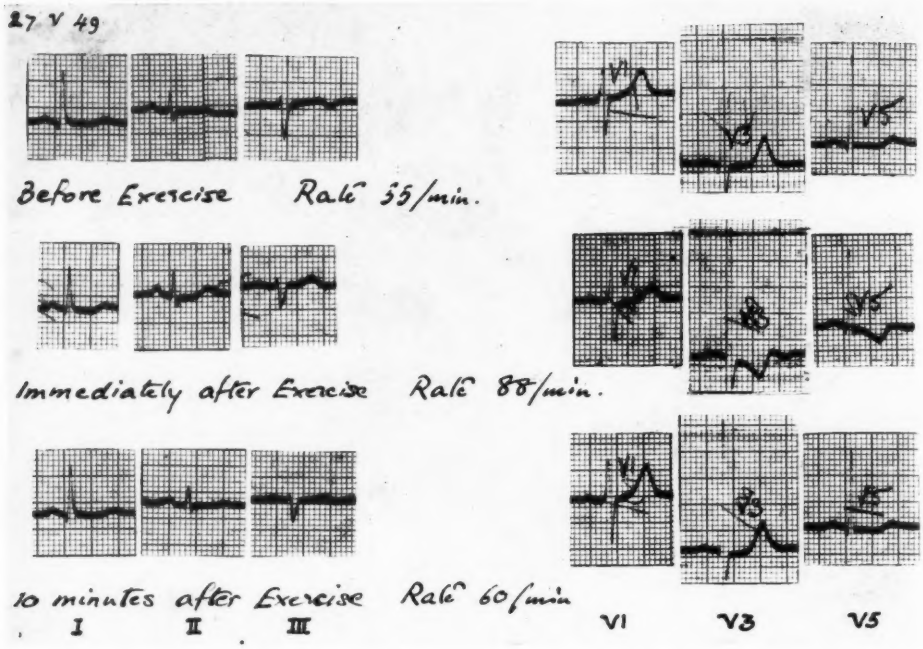

FIG. 3.—Case with evidence of myocardial ischæmia on exercise during the prodromal period. EC during prodromal period. Ischæmic change on exercise: S–T depression in V3 and diphasic T in V3.

attack. His hæmoglobin was 15·5g. per 100 ml. and his blood Wassermann reaction was negative. Immediate anticoagulant therapy with dicoumarol was started. The patient continued to have frequent short anginal attacks in bed, but these were always relieved by trinitrin tablets.

Electrocardiograms were taken daily and a series of ischæmic changes noted, the S–T segment in V3 first rising with a terminal biphasic T wave and the development of a very small Q wave. A graph taken after trinitrin showed more upright T waves in all chest leads and also a change in the QRS pattern in V3, which was considered to be due to altered position of the electrode. In the next graphs, taken at two-day intervals, there were no significant changes.

A week later, there was a further minor clinical incident, the patient complaining of mild but prolonged chest pain. An electrocardiogram showed the classical picture of an acute antero-septal myocardial infarct with a QS deflection in V3 and S–T coving with inverted T wave.

His general condition gradually deteriorated. There was no major prolonged anginal attack, but the signs of early congestive heart failure developed. The erythrocyte sedimentation rate rose steadily from a normal level on admission, while the white cell count fell; the blood pressure, though labile, also tended to fall. A low pyrexia developed during the last two days of life. He died suddenly on the eighteenth day after admission. Anticoagulant therapy had been continued uninterruptedly with satisfactory therapeutic prothrombin levels from the time of admission until death.

At post-mortem examination two points were looked for with especial interest; first, the exact age of the myocardial infarction in view of the prodromal ischæmic cardiographic changes; secondly, the nature of the slow occlusive process in the coronary arteries giving rise to this prolonged myocardial ischæmia. An extensive infarct of the left ventricle and septum was found, the

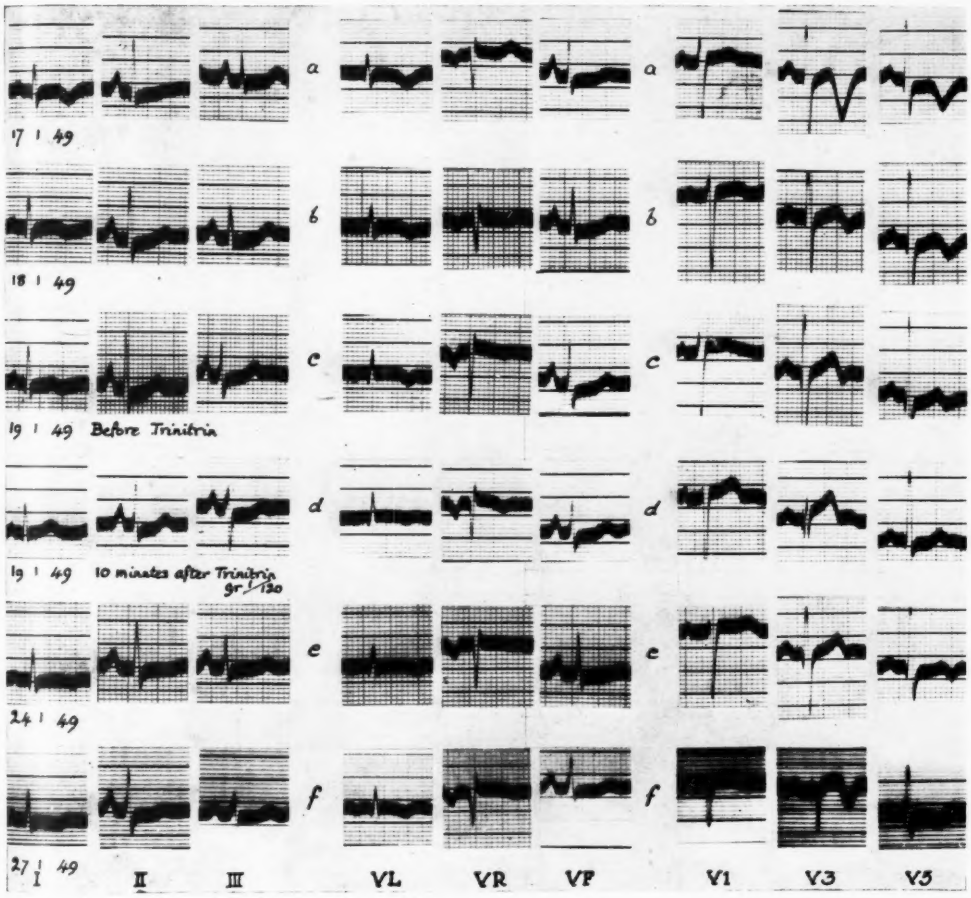

FIG. 4.—Case A. K., with evidence of myocardial ischæmia at rest during the prodromal period. (a)–(e) Cardiograms during prodromal period showing changing ischæmic patterns: S–T elevation in V1 and V3. No definite pathological Q waves. T wave inversion in V3 and V5. (f) Acute anteroseptal myocardial infarction.

whole of the infarct appearing to be of the same age both on macroscopic and microscopic examination. The muscle fibre was visible as muscle but was a pale buff colour and softer than normal. There was no evidence of fibrosis either in the infarcted areas or elsewhere, and no areas of greater softening or endocardial thrombosis. In the ascending aorta, evidence of syphilitic aortitis was seen but there was no stenosis of the mouths of the coronary arteries. The right coronary artery was almost completely occluded by old, healed atheroma and thrombosis; the left circumflex was atheromatous but patent. The descending left coronary artery (Fig. 7 and 8) was occluded 6 mm. below its origin by fresh purple-red thrombus only lightly adherent to the wall; below this the vessel was of good calibre. Histology here showed the arterial lumen to be partly narrowed by old healed atheroma and thrombosis; inside this a healing mural thrombus was seen, infiltrated with fibroblasts and containing strands of true collagen. On top of this there was a further layer, nearly closing the lumen, of very recent fibrin with entangled leucocytes and a few red cells.

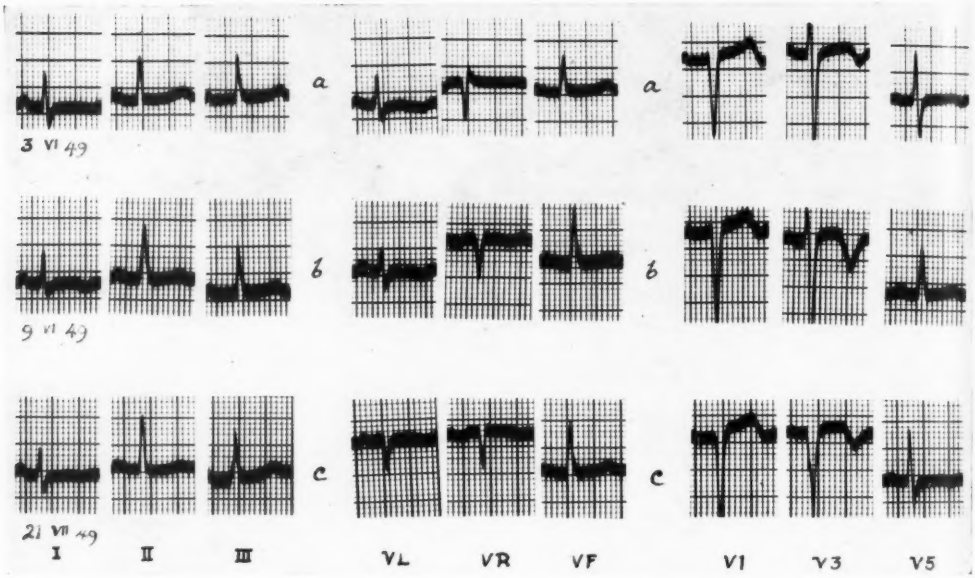

FIG. 5.—Case with evidence of myocardial ischæmia at rest during the prodromal period. (a) and (b) Cardiograms during prodromal period. Changing ischæmic patterns; slight elevation and coving S–T in V3; sharp symmetrical inversion of T in V3; no pathological Q waves; chest leads, one and two spaces up, also taken, but not illustrated here. (c) EC shows acute anteroseptal myocardial infarction.

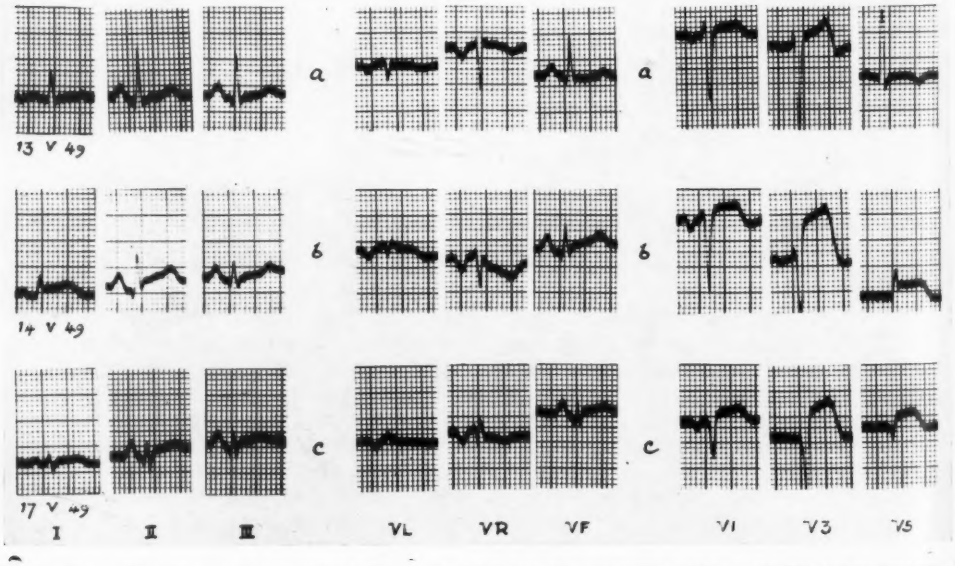

FIG. 6.—Case with evidence of myocardial ischæmia at rest during the prodromal period. (a) EC during prodromal period; ischæmic pattern. S–T elevation in V3 with diphasic T in V3 and T inversion in V5. (b), (c) EC shows acute extensive anterior myocardial infarction.

It was thought that the mural thrombus undergoing organization in the left descending coronary artery corresponded with the onset of symptoms five weeks before death and that the superimposed recent thrombus and the myocardial infarct were terminal and probably twenty-four to forty-eight hours old.

In a second case, a rather similar pathological picture was seen.

In the remaining two cases, evidence of a different pathology in the coronary arteries was found. In one, there was severe generalized coronary atherosclerosis with old occlusion of the left recurrent coronary artery and recent thrombotic occlusion of the right recurrent coronary artery which had previously supplied the collateral blood supply to the ischæmic area of muscle on the posterior wall of the left ventricle. The thrombus appeared to be of uniform age. Sections of the posterior wall of the left ventricle showed all stages of recent infarction from early necrosis up to absorption of fibres and also patches of old fibrosis. In the other case, in the wall of the left circumflex coronary artery hæmorrhage into an atheromatous plaque was seen (Fig. 9 and 10) which appeared to have ruptured into the lumen of the artery. From the point of rupture strands of fibrin radiated outwards into the fresh thrombus, which totally occluded the vessel lumen, as

FIG. 7.—Case A. K., transverse section of the descending branch of left coronary artery 6 mm. below its origin. Magnification, ×24. For explanation of A, B, C, and D see legend to Fig. 8.

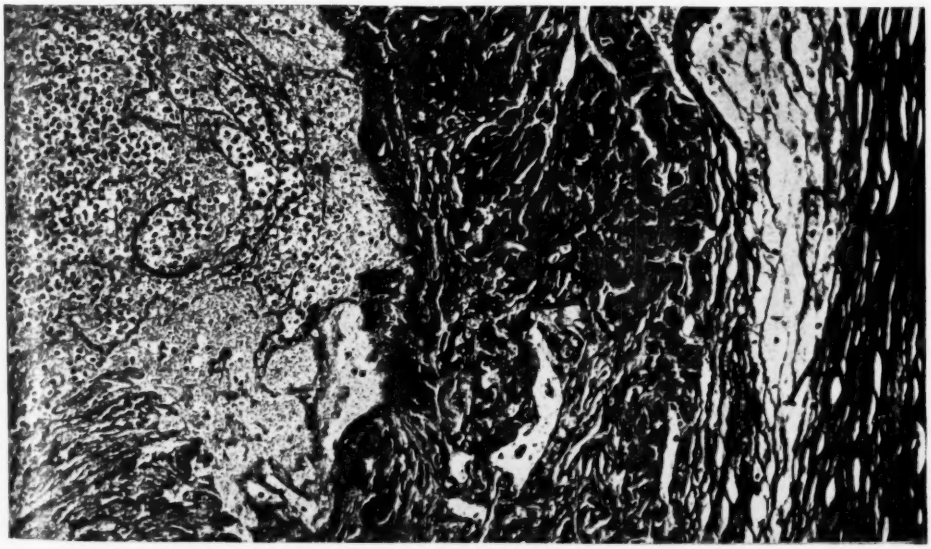

FIG. 8.—Higher power of same section as Fig. 7. Magnification, ×145. (A) old atheroma; (B) healing mural thrombus infiltrated with fibroblasts and containing strands of collagen; (C) very recent fibrin with entangled leucocytes and a few red cells; (D) fresh thrombus. (D) is shown in Fig. 7 only.

FIG. 9.—Transverse section of the proximal portion of the left circumflex coronary artery. Magnification, ×27.

FIG. 10.—Higher power of same section. Magnification, ×190.

Key to Fig. 9 and 10: (A) severe atheroma; (B) atheromatous "abscess"; (C) hæmorrhage into atheromatous plaque; (D) interruption of intimal wall; (E) strands of fibrin radiating from D into fresh unorganized thrombus occluding vessel lumen.

though the thrombus had grown from this point. In addition, a non-occlusive mural thrombus was seen in the left descending coronary artery. There was extensive recent infarction of the posterior wall of the left ventricle, in which different stages of infarction were seen. It is suggested that in the first case, slowly increasing arterial narrowing by atherosclerosis gradually reduced the blood supply to an already ischæmic zone of myocardium and caused recurrent localized muscle necrosis, and that the onset of prodromal symptoms corresponded with this terminal phase in a case of progressive coronary atherosclerosis. In the other case, the hæmorrhage into the atherosclerotic plaque was almost certainly the immediate precursor of the final thrombotic occlusion of the artery, but probably antedated it by not more than a week, since the red cells in it appeared well preserved. The onset of prodromal symptoms, a fortnight before that, may have been due to the older non-occlusive mural thrombus in the left descending coronary artery.

DISCUSSION

The incidence of prodromal pain in this series of cases of myocardial infarction was 29 per cent. This is lower than that of Sampson and Eliaser and of Feil, in whose series it was 48 per cent and 50 per cent respectively. Yater, in a series of men under 40, found an incidence of 9·5 per cent. Many different factors may account for this difference: the errors inherent in statistics applied to small groups, clinical and electrocardiographic criteria for inclusion of cases and also possibly variation in the recording of the symptomatology of the disease.

The fatality rate in this series in the prodromal group, without taking into account histories of

previous coronary occlusions, was 15 per cent compared with 34 per cent and 43 per cent in Sampson and Eliaser's and Yater's series respectively. The fatality rate in the group without prodromal symptoms was 50 per cent both in the present series and in that of Sampson and Eliaser; in Yater's series it was 53 per cent for the total group of cases of myocardial infarction reviewed. The figures in the three series vary widely, but in all reports there was a lower fatality rate in the prodromal group than in the group without prodromal symptoms.

In previous series, the use of electrocardiograms of only standard leads detracts greatly from their value at the present time. Electrocardiographic changes that occur during the prodromal period can today be better assessed by full unipolar lead exploration in addition to the standard leads. It is noteworthy that in the present series, in the prodromal pain group, some patients showed evidence of severe myocardial ischæmia at rest and that, of those who had a negative resting graph, no patient on whom an exercise test was performed failed to show evidence of ischæmia.

Results of erythrocyte sedimentation tests, white cell counts, temperature records, and blood pressure changes are not recorded here. Typical changes were observed after the occurrence of myocardial infarction. Results obtained during the prodromal period were usually negative, although minor changes were sometimes observed. In all cases in the prodromal group, the hæmoglobin was within normal limits. The blood Wassermann reaction was positive in one case only, in whom there was no clinical or radiological evidence of syphilitic aortitis and the electrocardiographic diagnosis of myocardial infarction certain.

Post-mortem findings in this series offered evidence to support the concept that the cause of prodromal pain is a gradually decreasing lumen in a coronary artery with consequent increasing myocardial ischaemia, finally culminating in myocardial infarction with coronary occlusion. Such a pathological process, whether the occluding arterial lesion be a growing thrombus, subintimal hæmorrhage, atheromatous plaque, or gradual sclerosis, forms a reasonable explanation for the development of atypical angina pectoris as a prodromal symptom in myocardial infarction.

SUMMARY

Earlier studies of prodromal symptoms in myocardial infarction are briefly reviewed and the relation of this syndrome to " coronary failure " discussed.

A series of 40 cases of myocardial infarction with prodromal symptoms is described, in which most cases suffered prodromal symptoms *de novo*, but in which a few experienced a new type of anginal pain following on a long history of typical angina of effort.

The clinical and electrocardiographic features are described.

The necropsy findings support the concept that the cause of prodromal pain is a gradually decreasing lumen of a coronary artery with consequent increasing myocardial ischæmia, finally culminating in myocardial infarction and coronary occlusion.

The importance of the clinical diagnosis of this syndrome lies in the prophylactic treatment of myocardial infarction with rest and, possibly, anticoagulant therapy.

I am indebted to Professor McMichael for the facilities for carrying out this work and to both him and Dr. Wallace Brigden for encouragement and much helpful criticism. I am also indebted to Dr. C. V. Harrison for his criticism of the interpretation of the pathological sections and to Dr. Paul Wood for his criticism of some of the interpretations of electrocardiograms.

This paper is an abstract from a thesis submitted for the M.D. degree at Cambridge University, and I am indebted to Sir Lionel Whitby, Regius Professor of Physic, Cambridge University, for permission to publish it.

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THE MEASUREMENT OF BLOOD FLOW BY THE LOCAL CLEARANCE OF RADIOACTIVE SODIUM

BY

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The study of the local clearance of radioactive sodium was initiated by Kety (1948) who suggested that the rate of loss of local radioactivity reflected the local effective blood flow. The method has, up to date, been used for the study of blood flow in muscle (Kety, 1949; Cooper *et al.*, 1949 and Cooper, 1949) and it was shown that after application of a tourniquet to check the arterial inflow the number of counts per minute remained constant. On release of the tourniquet there was a rapid decline in the counts per minute attributed to the reactive hyperæmia. As the counts thus apparently reflected both the cessation of the circulation while the tourniquet was applied and the subsequent increase on its release, the method was thought suitable for the relative determination of effective local blood flow and useful for studying the circulation in particular in the skin and viscera (Kety, 1949). Obviously such a method would be convenient and simple for the investigation of circulation in organs otherwise inaccessible for circulatory studies. Before such extensive use it is, however, essential to ascertain that the method is capable of determining with reasonable accuracy changes in effective local blood flow. Experiments involving the use of a tourniquet on a limb were not considered sufficient evidence for this assumption, and further investigations on the local clearance of radiosodium in skin and muscle are accordingly presented.

METHOD

The procedure is essentially that described by Kety (1949). The Na_{24} was prepared in isotonic sodium chloride solution. In the investigation of the skin the injection contained between 2 and 3 microcuries of Na_{24} and was adjusted by dilution with isotonic saline to a volume of between 0·05 and 0·15 ml. This was injected either intradermally to raise a wheal or slightly deeper into the cutaneous tissue. A slight leak back of fluid and blood along the needle track might occur and it was important to wash this off and not to place the Geiger-Muller counter in position until the aperture in the skin had sealed. In the investigation of muscle the depot was placed at 2 cm. depth and accordingly the activity of the solution was increased to about 5 microcuries and the volume to between 0·2 ml. and 0·5 ml. Counts were recorded over periods of 30 seconds at minute intervals and the results have either been plotted semilogarithmically or expressed as the clearance constant as defined by Kety (1949). This constant is proportional to the rate of disappearance of the radiosodium from the depot.

To ascertain the changes in the skin circulation the heat elimination of the hand was measured in a calorimeter of the improved pattern described by Greenfield and Scarborough (1949). The injection of radiosodium was made either into the opposite hand and the counter placed in contact with the skin or into the hand inserted in the calorimeter. In the latter case the counting was carried out through the wall of the vacuum flask; this ensured that the calorimetric and radiosodium measurements were made under identical local conditions though the hand could not be held so

steady as when supported outside on a sandbag. Alterations in skin blood flow were produced by immersing either the feet or the free upper limb in water at 44° and 15° C. Variations in skeletal muscular blood flow were brought about by the intravenous infusion of synthetically prepared lævo-adrenaline in a dose varying from 5 to 30 μg. a minute. Before the observations were begun a saline drip was established and through a Y connection either normal saline or saline containing adrenaline was infused.

Results

In investigating the cutaneous circulation, the depot of radiosodium was placed in the dorsum of either the hand in the region of the knuckles or the middle or distal phalanx of the middle finger. In the first instance, the clearance rates were studied at room temperature (19°–22° C) and in response to indirect heating and cooling. Little alteration was noted in the clearance constant though it was considered that these procedures were sufficient to cause large alterations in cutaneous blood flow. These results were accordingly compared with simultaneous observations made with the calorimeter.

TABLE I

Comparison of Heat Elimination and Local Clearance of Radiosodium in the Hand

Experiment No.	Preliminary		Full reflex vasodilatation		Reflex vasoconstriction	
	Heat elimination cal./min.	Clearance constant	Heat elimination cal./min.	Clearance constant	Heat elimination cal./min.	Clearance constant
1	103	0·021	332	0·025	95	0·018
2	164	0·030	290	0·023	81	0·030
3	244	0·051	300	0·039	217	0·023
4	110	0·067	333	0·064	82	0·035

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The results in all the experiments involving skin blood flow are shown in Table I. Fig. 1 shows the changes in heat elimination in one hand and in radiosodium counts in the other hand when the feet were placed in hot and cold water. Fig. 2 illustrates an experiment in which the calorimetric observations and radiosodium counts were made in the same hand. In all the observations the results were similar. During the initial period a steady local clearance of radiosodium was observed and we confirmed that this clearance could be completely checked by inflating a cuff round the upper limb above systolic pressure. Little change in the rate of local clearance of Na_{24} was observed when full reflex vasodilatation had been produced by the indirect heating. Though the heat elimination might be increased threefold or more, the clearance constant showed only a slight, or no increase. Reflex vasoconstriction produced by cold water led to an immediate reduction in the heat elimination and to a decrease in the clearance constant. These findings were constant irrespective of the site or depth of the radiosodium injection in the hand or finger.

In resting muscle, clearance constants similar to those reported by other workers have been obtained. The results are shown in Table II. The clearance was stopped by a cuff inflated above the arterial pressure and release of the pressure was followed by a period of removal of the radiosodium at a higher rate (Fig. 4). Intravenous infusion of adrenaline in doses up to 30 μg. a minute in six experiments (Table II) produced only a slight increase or no significant change in the clearance constant (Fig. 3 and 4). The adrenaline used was shown to be active by the development of marked pallor of the face and palpitations, and by the characteristic changes in the pulse rate and blood pressure.

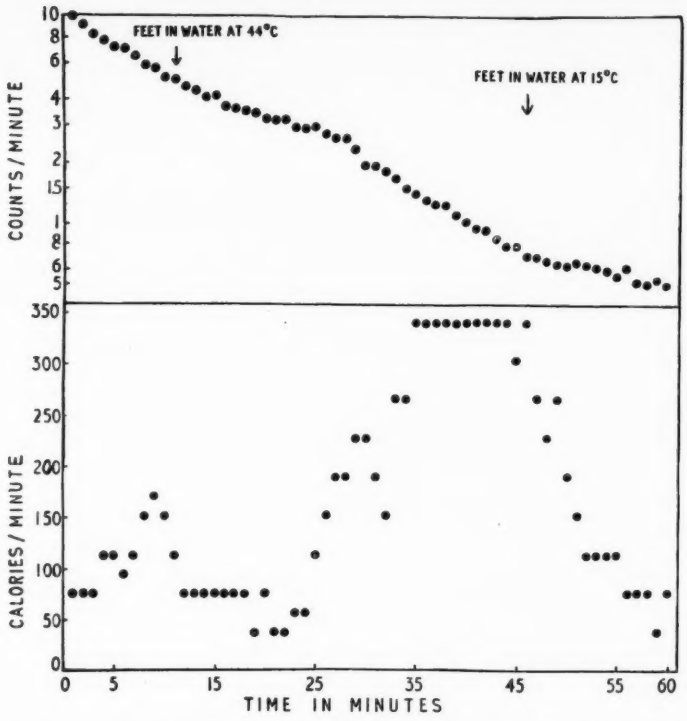

FIG. 1.—Simultaneous measurement of the clearance of a depot of radiosodium in the skin of the dorsum of the left middle finger and of the heat elimination from the right hand. At the points marked the feet were placed in hot and cold water. The considerable changes in heat elimination were not associated with any conspicuous corresponding changes in radiosodium clearance.

TABLE II

THE EFFECT OF INTRAVENOUS ADRENALINE INFUSIONS ON THE CLEARANCE OF RADIOSODIUM IN MUSCLE

Experiment No.	Saline infusion	L-Adrenaline infusion	
	Clearance constant	Dose μg./min.	Clearance constant
5	0·051	5	0·048
6	0·053	15	0·041
7	0·048	20	0·057
8	0·133	20	0·140
9	0·041	25	0·055
10	0·064	30	0·060

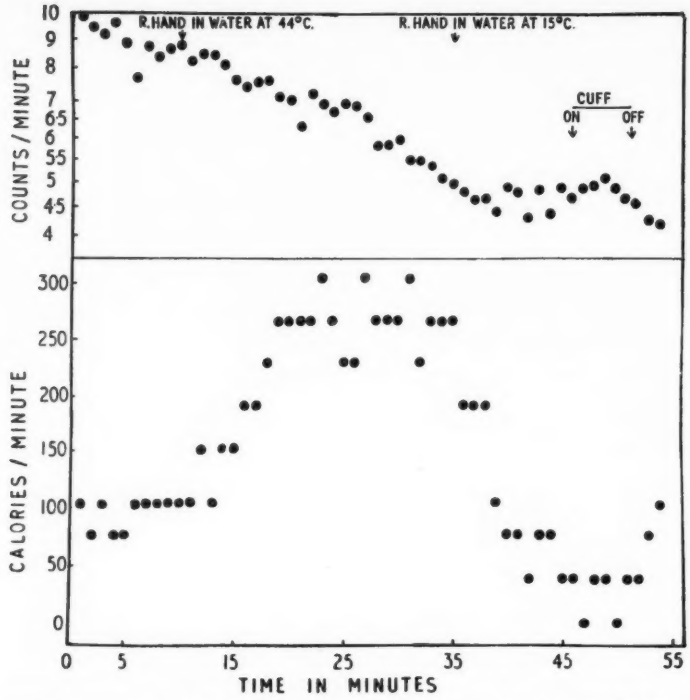

FIG. 2.—Simultaneous measurement of the local clearance of a depot of radiosodium in the skin of the left middle finger and of the heat elimination from the left hand. The circulatory changes resulting from placing the right hand in hot and cold water and from inflation of a cuff on the left arm are shown.

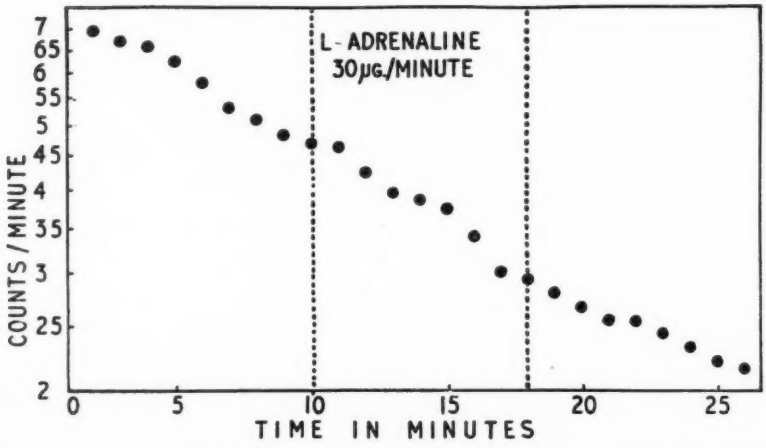

FIG. 3.—Local clearance of a depot of radiosodium in the calf muscle. The intravenous infusion of adrenaline at a high rate did not appreciably increase the rate of removal of the radiosodium.

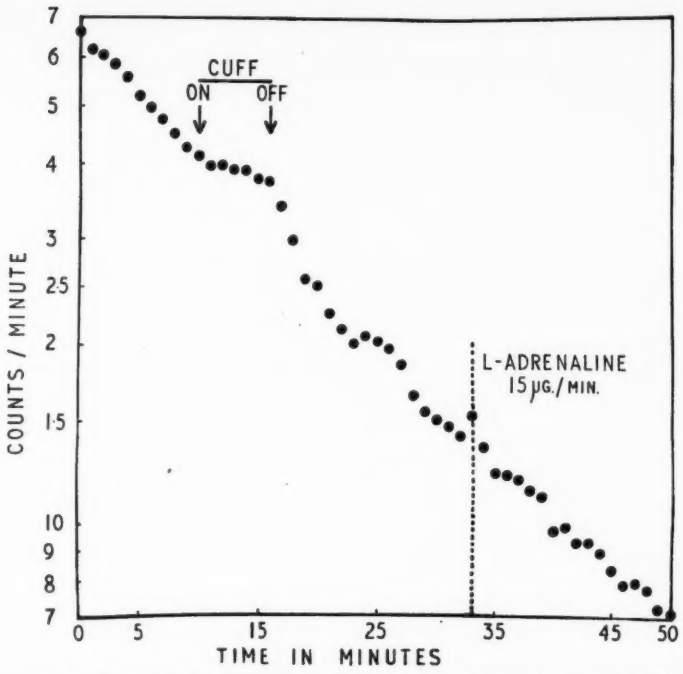

FIG. 4.—Local clearance of a depot of radiosodium in the forearm muscle showing the effect of inflation of a cuff on the arm and of an intravenous infusion of adrenaline. The removal of radiosodium is checked by the tourniquet but not increased by intravenous adrenaline.

DISCUSSION

The local clearance of radiosodium depends on many factors which have been enumerated by Kety (1949). Removal by lymphatics is probably negligible and if this quantity is disregarded and local diffusion in the tissue planes is slight, the clearance is determined by the rate at which the radiosodium is removed in the blood vessels. This must depend on the rate of exchange of sodium between the depot and the plasma within the capillaries and the number of patent functioning capillaries in the vicinity of the depot. The velocity and volume of flow in patent capillaries can only be of importance in so far as they expedite the transfer of radiosodium from the depot to the vessels.

In the skin the failure of the clearance constant to increase during a period of reflex vasodilatation may be due to the blood passing through arteriovenous anastomoses and thus being ineffective as far as tissue exchanges are concerned. It should, however, be noted that reflex vasoconstriction was associated with a decrease in the clearance constant. This decrease was immediate and thus not secondary to cooling of the part and consequent reduction in local metabolism. Furthermore, the prompt reduction was also observed when the counting was done on the hand in the calorimeter and any local cooling could thus be excluded. Our results thus suggest that the clearance of radiosodium in skin is not solely a measure of effective circulation as determined by local tissue metabolism. It is reduced by reflex vasoconstriction but little affected by reflex vasodilatation.

The method was no more satisfactory as a means of studying variations in blood flow to skeletal muscle. Intravenous infusion of adrenaline is known to produce a conspicuous vasodilatation in skeletal muscle, and at the onset of the infusion there is an enormous transitory increase in the blood flow; thereafter the blood flow falls slightly but is maintained at a rate considerably above the resting level (Allen *et al.*, 1946). These features were not closely reflected in the clearance rates of radiosodium which were only slightly increased or unaffected by the adrenaline infusions. These changes were within the experimental error of the measurements. The vasodilatation caused by adrenaline is associated with a reduction in the muscle glycogen content and a rise in the blood sugar level (Hildes *et al.*, 1949). This transfer of carbohydrate indicates that an active exchange between muscle and blood stream is taking place; a greatly increased clearance of the radiosodium depot would have been anticipated if the method were measuring accurately muscle blood flow. In the tourniquet experiments during the period of cessation of the arterial circulation, radiosodium is presumably accumulating in the local capillaries and on return of the circulation this unduly high concentration is swept away. The increased clearance rate immediately after a period of ischæmia is thus not sufficient evidence that the clearance of a depot of radiosodium reflects closely blood flow to the tissues under different circumstances.

We thus see that the method, though convenient and easy to use, is relatively insensitive when checked by other methods that are known to measure more accurately alterations in blood flow. It is very doubtful if it is sufficiently sensitive to give information of value regarding blood flow in pathological states of the limbs or in deeper organs where no alternative method is available for comparison.

Summary

The local clearance of radiosodium injected into skin and muscle has been studied. The observations that application of an arterial tourniquet checked the removal of the radiosodium and that release of the tourniquet was followed by a period of increased rate of clearance were confirmed.

The rate of removal of radiosodium injected into the skin of the hand was not increased by vasodilatation produced by indirect heating but was diminished by reflex vasoconstriction.

Intravenous infusion of lævo-adrenaline produced no significant alteration in the rate of clearance of radiosodium injected into skeletal muscle. The clearance rate in these circumstances did not reflect closely the changes in local blood flow to the muscle.

We wish to thank Professor E. J. Wayne for his helpful criticism and encouragement; and Miss L. Fearn for technical assistance with the counting equipment.

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THE VECTORCARDIOGRAM IN 100 HEALTHY SUBJECTS USING A NEW DRAWING INSTRUMENT

BY

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The development of electrocardiography has led to the recording of the potentials produced by the heart at an increasing number of sites on the body surface by various combinations of leads. This trend has focussed attention on greater numbers of patterns, with emphasis on more and more detail. Pari passu with these developments, many investigators have endeavoured to record and interpret the central electrical field of the heart as a whole.

Mann (1920) showed that a single continuous curve could be obtained by the fusion of three leads into a monocardiogram. He constructed the curve from direct voltage measurements at equal and successive time intervals from standard leads ; simultaneous QRS complexes were not measured, but Mann considered that this did not introduce a serious error. Eighteen years later, Mann (1938) described a moving-coil galvanometer that could respond in two planes to the potentials from two leads, and the resulting loop was recorded photographically. This technique has not been generally accepted.

Schellong (1936) and Wilson and Johnston (1938) independently showed that the cathode-ray tube could be used to produce a continuous curve from the amplified voltage of extremity leads; they preferred to call this loop a vectorcardiogram. Wilson and Johnston and others employed leads based on the Einthoven triangle to record the vectorcardiogram in the frontal plane, and more recently a central terminal placed at the back has been used to provide reference in depth to form a tetrahedral system.

Duchosal and Sulzer (1949) have made extensive contributions to this subject using cathode-ray apparatus with a split electron beam, thus enabling simultaneous loops from the frontal and saggital planes to be recorded. They have used a parallelepiped reference system.

The slow development of vectorcardiography has been in some measure due to the elaborate and time-consuming nature of these methods. Grant (1950) has recently sought to overcome this difficulty by drawing or envisaging the curve from an inspection of standard and præcordial leads; his method is an approximation and no integrating apparatus is used. As the principal application of vectorcardiography is likely to be in the field of myocardial disease where conventional electrocardiography already shows a high degree of correlation with pathological findings, it would seem desirable to retain at least the degree of accuracy obtained in recording the scalar electrocardiograms.

The mathematical and physical approach that has been used by some authors to treat the fundamental problems of this subject is recognized to be of great importance; however, it may be that such esoteric analyses have also tended to slow the application of vectorcardiography to clinical medicine. It appears to us that the inherent errors in methods that on the one hand employ accurate electronic recording devices and on the other hand are concerned with such biological variables as skin resistance, tissue conductivity, chest shape, and heart position deny an elaborate mathematical analysis which, at best, gives greater definition to the subject than it actually has. Our limited experience of vectorcardiography has not enabled us to form any firm conclusions and it must be stated that our approach has been entirely empirical.

The high cost of electronic apparatus, the difficulties of maintenance, and the time consumed in operation, all limit its use at the present time in this country. Our aim has been to develop a simple method for obtaining vectorcardiograms which might be applied to routine clinical work. In this paper we describe an apparatus by means of which the two-dimensional projections of the spatial vectorcardiogram in each plane may be drawn quickly from the appropriate leads of any reference system, and we present an analysis of the vectorcardiograms obtained by this method from 100 healthy adults.

The Apparatus

The integrating apparatus consists of a scanning table which is joined by control cables to an optical head. The two parts are mounted on the same stand. (Fig. 1).

The Scanning Table. A four-inch square of perspex sheet is mounted on a rack and pinion to form a mechanical stage, which is fixed near to the front of a wooden base so that the perspex stage may be racked in a front-to-back direction (Fig. 2). The elctrocardiogram is held to the stage by clamps.

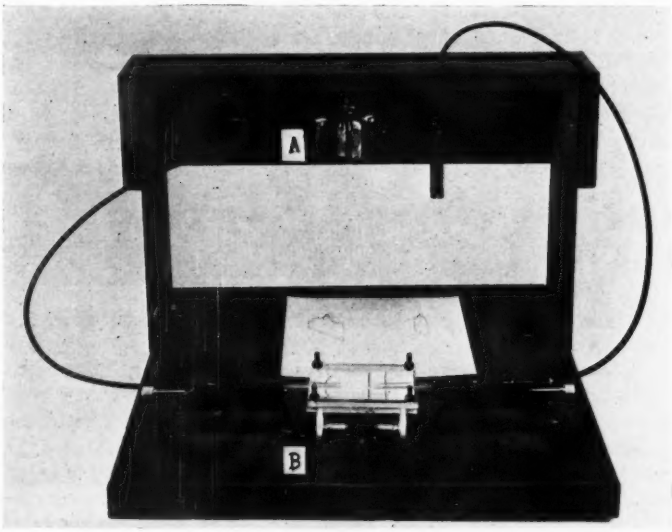

Fig. 1.—The vector drawing machine. (A) Optical head. (B) Scanning table.

Fine-adjustment mechanical stages, of the type used in the mechanical stage of a microscope are mounted on short legs secured to the base on either side of the perspex stage. Perspex fingers ($3 \times 0{\cdot}5$ in.) are attached to the upper movements of these stages so that they project over the scanning table and may be moved across the table from side to side by the mechanical stages. Each of the transparent fingers has a central and cross-hair line so that the voltage curve of the two underlying synchronously recorded electrocardiograms may be followed. The ends of the control cables are fixed to angle brackets which are mounted on the sides of each fine-adjustment stage. A spring-loaded screw thread with thumb screw enables a fine adjustment to be made on the cable length for the purpose of centering the light spot.

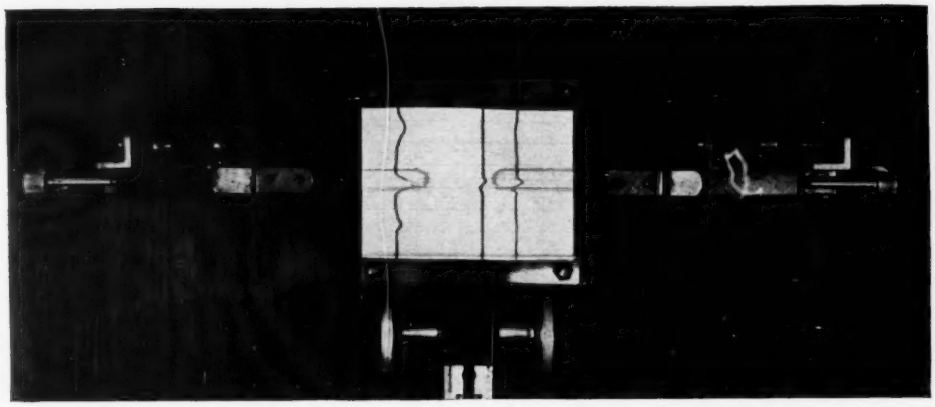

FIG. 2.—The scanning table. Perspex fingers are overlying the QRS complex of leads A and B.

The Optical Head. This is mounted on a wooden gantry twelve inches above the baseboard (Fig. 3). The light of a flashlamp bulb is reflected by means of a right-angled prism through a plano-convex lens (Fig. 4) on to the first of a pair of surface-silvered mirrors. This mirror is mounted at right angles to the gantry and may be turned by means of a 2·5-inch lever to which is attached the end of one of the spring-loaded control cables. Rotation of this mirror is produced by movement of the left-hand mechanical stage. The light is reflected off this first mirror on to a second mirror placed close to and at right angles to the first, and it is so arranged that the beam is reflected on to a sheet of paper placed directly below the gantry and optical head. The mounting of the second mirror is similar to the first and it is moved by the control cable from the right-hand mechanical stage. Movement of the left-hand stage will cause the light spot on the base to move in a back-to-front direction, and that of the right-hand one in a side-to-side direction.

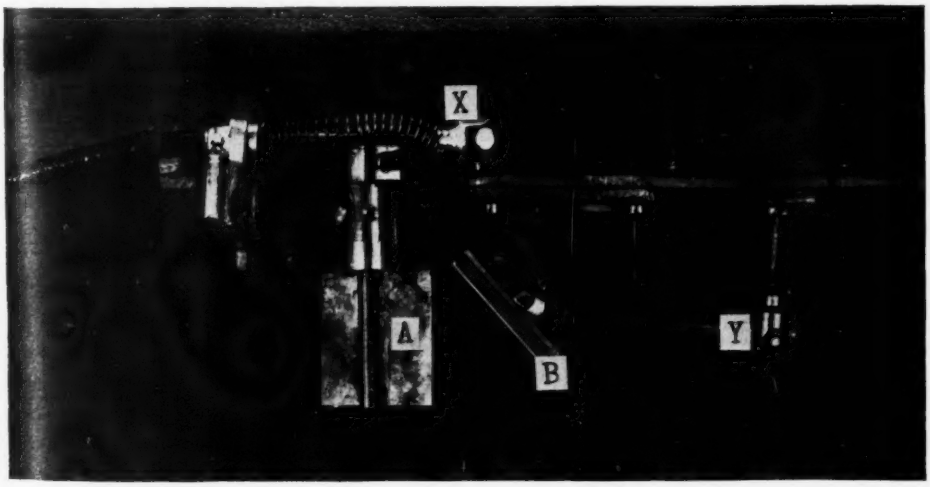

FIG. 3.—The optical head. Showing the two mirrors A and B and their respective levers X and Y.

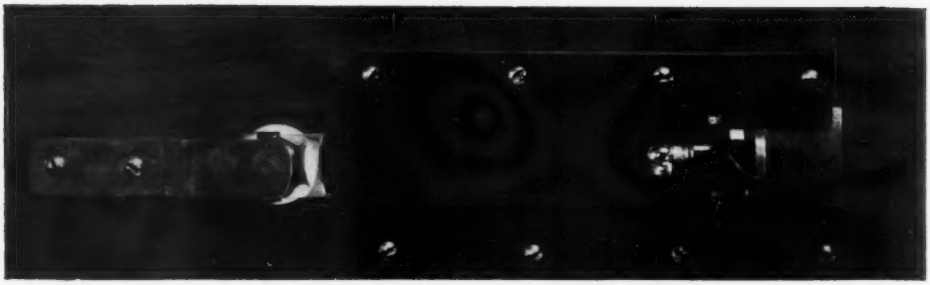

FIG. 4.—Light source and reflecting prism at the back of the optical head.

Thus it will be seen that the voltage curve of two synchronously recorded scalar electrocardiograms may be scanned by each of the perspex fingers at progressive time intervals. These fingers move the mirrors and cause a deflection of the light beam which is an integration of the two movements; this might be compared with the deflection of the electron beam by the plates of the cathode-ray tube of more elaborate apparatus.

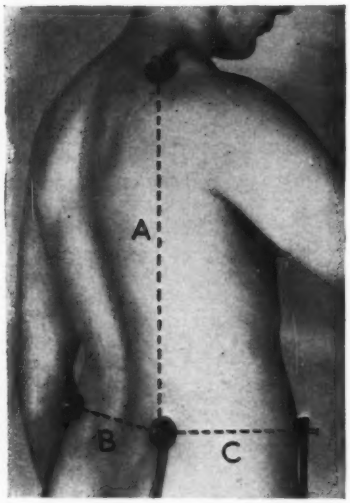

FIG. 5.—Electrode positions. A, B, and C indicate the bipolar lead connections.

METHOD

(1) *The Scalar Electrocardiogram.* All records were taken with an Elmquist three-channel electrocardiograph which consisted of valve amplifiers with resistance capacity coupling and oil-damped mirror galvanometers, and had a frequency response almost linear to 400 cycles.

The box-shaped reference system recommended by Duchosal has been used throughout. An electrode common to the three bipolar leads to be recorded is placed over the right posterior iliac spine, and the first exploring electrode over the upper part of the right scapula; the second exploring electrode is placed over the right anterior superior iliac spine and the third over the left posterior iliac spine (Fig. 5). (These are the CR lead connections on the Elmquist machine with the right-arm connection as the common electrode.)

The simultaneous electrocardiographic tracings were made at a standardization of 1·5 cm. to 1 millivolt, and at a paper speed of 120 mm. a second. These factors were determined arbitrarily so that the QRS was of sufficient size to make mechanical scanning of the time intervals at 1/200th of a second simple and accurate.

We have used the apparatus described to draw the frontal, sagittal, and horizontal loops of the QRS and T complexes from the scalar electrocardiograms obtained by this method. In every case limb leads and chest leads were taken for purposes of comparison.

(2) *Integration into the Vectorcardiogram.* A short strip of the simultaneously recorded scalar electrocardiograms is clamped on to the scanning table so that the isoelectric lines lie in a front-to-back direction, and the tracing obtained from the vertical lead is to the left (Fig. 2). The cross-wires are placed at a point on the isoelectric lines of the vertical and transverse leads (A and B). The light spot is turned on and a sheet of paper placed centrally below the optical head; on this

sheet there are ruled vertical and horizontal lines which represent zero potential (Fig. 6). The light spot is moved by the adjusting screws on the mechanical stages until it coincides with the upper left-hand intersection of the ruled lines. The adjusting screw of the scanning table is turned so that the longitudinal hair lines on the perspex fingers coincide with the beginning of the QRS complex. The stage is advanced by an amount recorded by 1/200th of a second on the time marking of the electrocardiogram. The mechanical stages are then reset so that the cross-hair lines follow the electrocardiographic tracing to the new voltage poition. The resultant new position of the light spot which has been deviated from the isoelectric lines is recorded by a pencil mark. The whole QRS and T complex is plotted by repeating this process at time intervals of 1/200th of a second. The positions of the light spot indicated by pencil dots therefore provide time markings and a line joining them forms a loop representing the frontal projection of the spatial vectorcardiogram. Likewise, the sagittal loop is drawn by integrating the electrocardiogram from the leads A and C and the horizontal from the leads B and C. The drawing paper is arranged so that the sagittal loop is to the right of the frontal, and the horizontal below it.

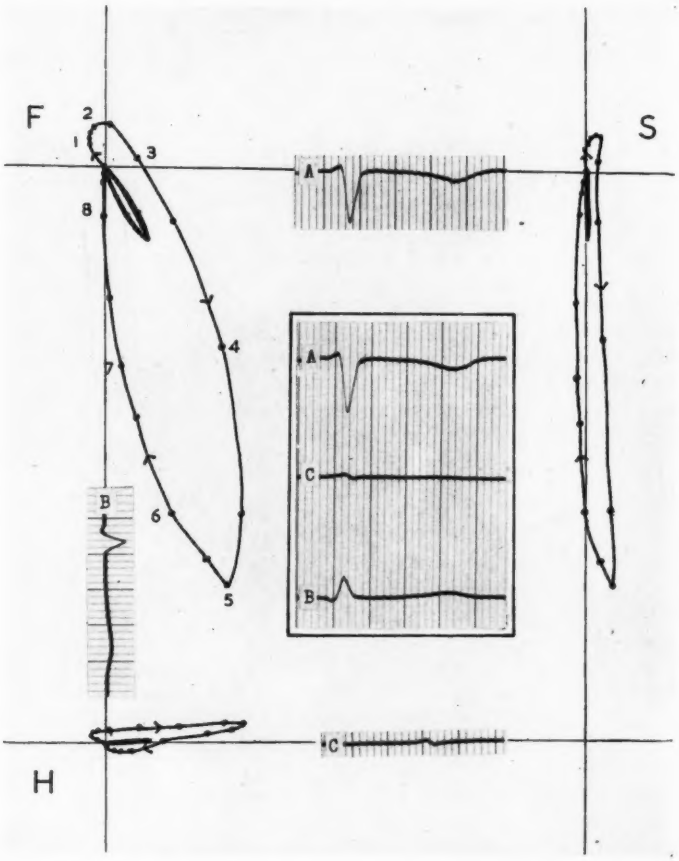

FIG. 6.—Frontal (F), sagital (S), and horizontal (H) projections of the spatial vectorcardiogram drawn from the three scalar electrocardiograms A, B, and C. The " T " loop is in heavy black. The figures denote 1/100th of a second and the arrows the directions of rotation.

Clinical Material

One hundred healthy adults were investigated and the majority were men; their ages were evenly distributed between 16 and 70. All were clinically examined and found to be without evidence of cardiovascular disease. Patients with a blood pressure over 160 systolic and 90 diastolic were not included. The electrocardiograms were recorded with the patient on a couch in a semi-recumbent position. Most of the younger group were drawn from medical students and medical staff and the older group were selected from otherwise healthy patients who were being treated for superficial neoplastic lesions by radiotherapy.

Results

The frontal, sagittal, and horizontal projections of the spatial vectorcardiogram in health were found to have characteristic features (Fig. 6 and 7). Their outline was smooth, with minor exceptions in some loops of the older age group. The rotation of the frontal loop was either in a clockwise or anti-clockwise direction. The length of the QRS loop varied from 0·06 to 0·1 sec. and the apex was reached in 0·03 to 0·05 sec. The time intervals tended to be closely spaced at the beginning and the end of the loop and spread out evenly in the middle of the tracing. In the horizontal loop several of the time interval marks were superimposed on the isoelectric line. The T loops tended to rotate in the same direction and their axis lay in, or within a few degrees of the QRS loop.

The spatial vectorcardiogram was a narrow loop in the frontal view and was directed downwards and slightly to the right. The greater part was in the lower right quadrant but in some cases the return loop extended for some distance up into one of the upper quadrants. The ratio of the height of the outgoing part to the depth of the whole loop never exceeded 1: 4.

In the sagittal view the tracing was also narrow and directed downwards and slightly to the right, and since the vertical component is common to the sagittal and frontal loops, extensions above and below the isoelectric were the same in both.

The horizontal spatial vectorcardiogram was narrow and small as compared with the frontal and sagittal views. Lead B is common to the frontal and horizontal loops so that the lateral extension of these loops was identical.

In the older age group, a few patients showed small kinks which were never large in comparison with the whole loop (Fig. 7C and 8B). Ten selected loops representing the limits of variation found in this series are shown in Fig. 8.

Comments

We have not concerned ourselves with any of the fundamental issues of vectorcardiography or the relative merits of various spatial reference systems, but it is possible that the methods we have used might be applied to some of these problems.

The technique described has the merit of simplicity and the apparatus is inexpensive. It requires no special knowledge or experience for its operation, the three loops may be drawn quickly and the results are comparable with those obtained by other methods. The tracings made by this method are clear and considerably larger than those produced on the cathode-ray tube, and the direction of rotation is easily determined. The scalar electrocardiograms may be recorded and stored, and the loops drawn subsequently; the individual QRS and T complexes may be drawn separately and remain quite distinct. If desired, the scalar electrocardiogram may be photographed at faster speeds and at greater amplification.

The error introduced by the distance between the mirrors and consequent difference in magnification of two scalar components is corrected by one of the mirror levers being slightly longer than the other. Any distortion produced at the edges of the field is small because the distance from the base to the optical head is large in relation to the size of the vectorcardiogram. We have found that

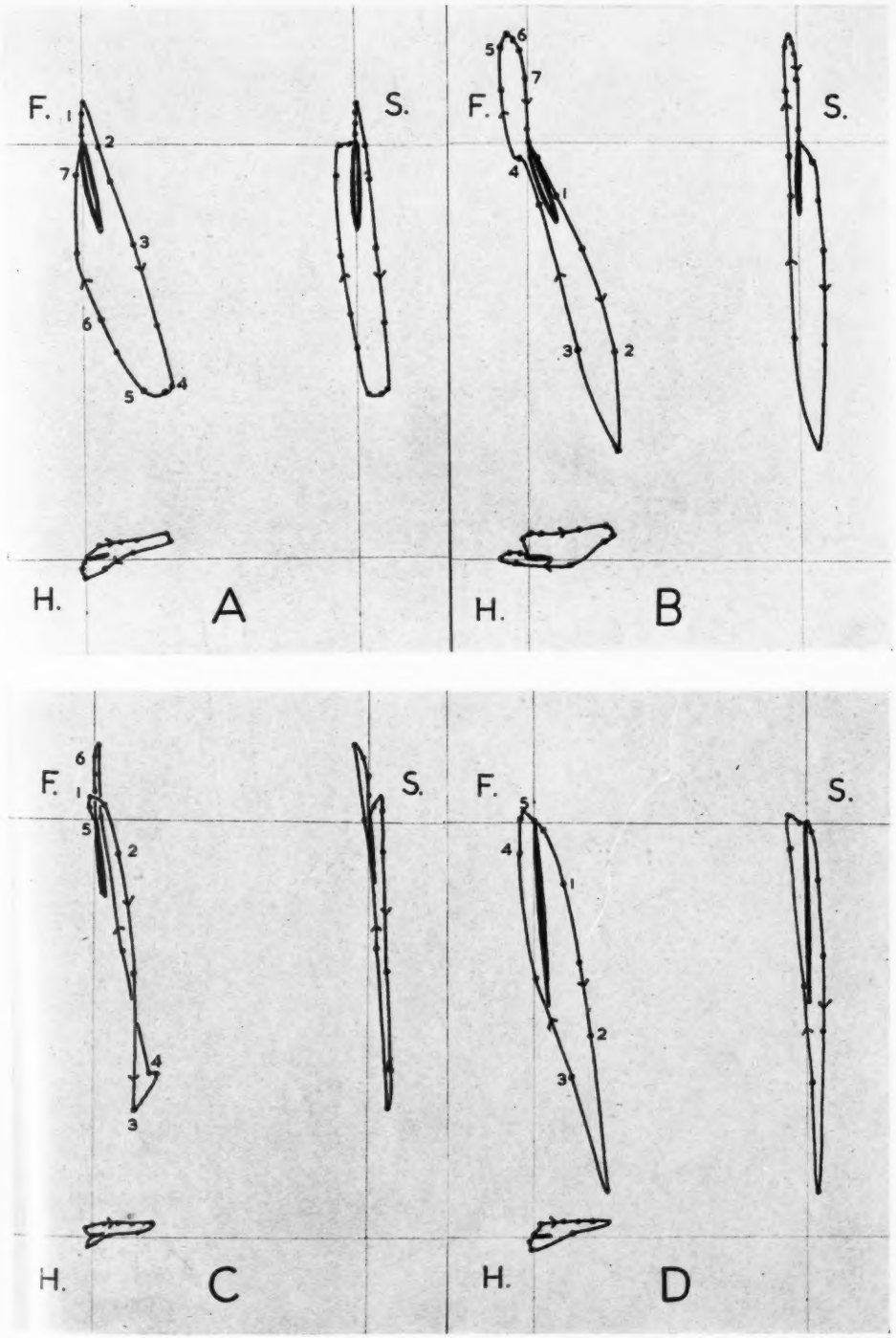

FIG. 7.—Examples of the vectorcardiogram in health: (A) shows a small upward projection on the outgoing part of the loop; (B) has the upward component on the returning limb; (C) shows a kink at 4/100ths of a second; and (D) a smooth loop with no irregularities.

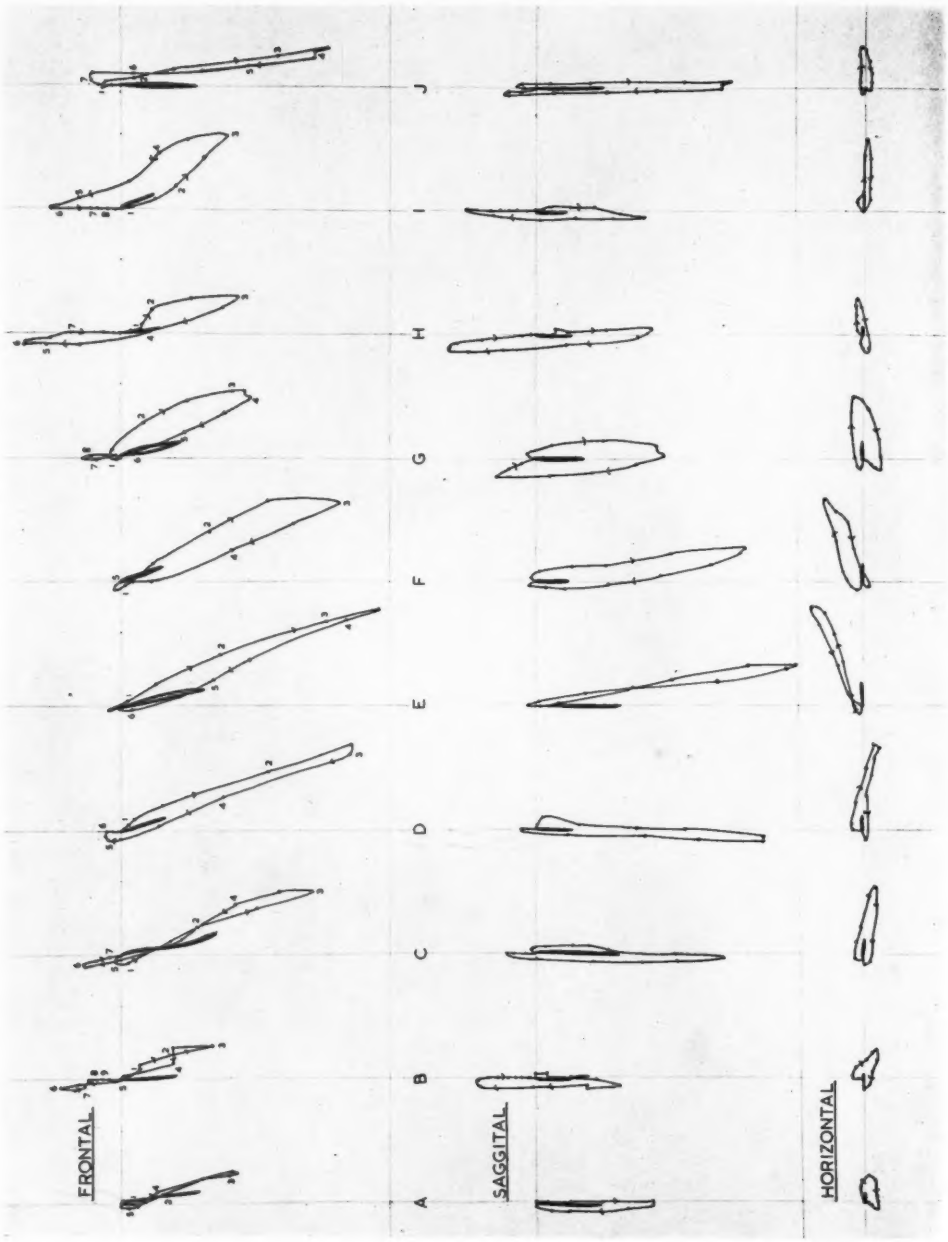

FIG. 8.—Ten vectorcardiograms to show the limits of variation in the series.

the spring loading of the control cables ensures that there is no backlash between the scanning fingers and the light spot.

The 100 healthy adults examined showed a variety of patterns, but these fell within limits that were not difficult to define. The patterns were similar to those obtained by Duchosal and Sulzer (1949) when allowance was made for different polarity and direction of viewing. The normal patterns obtained from the tetrahedral reference system and illustrated by Conway *et al.* (1949) were also similar to those seen in our series. We have not constructed three-dimensional models from the plane drawings of the vectorcardiogram; apart from their value for demonstration purposes, such models have not appeared to us to give information that could not readily be obtained from the drawings.

The loops were characterized by a smooth contour but a few from the older age groups showed slight irregularities or kinks although these patients were normal clinically. It is, perhaps, not irrelevant speculation to relate this loss of smoothness to degenerative changes in the myocardium.

FIG. 8.—Ten vectorcardiograms to show the limits of variation in the series.

SUMMARY

A new method of integrating scalar electrocardiograms in two planes is described. The apparatus relies on mechanical scanning of the electrocardiograms and their optical integration into a vectorcardiogram.

One hundred healthy subjects have been examined, using a parallelepiped reference system, and the scalar electrocardiograms thereby obtained have been integrated into frontal, sagittal and horizontal loops.

The vectorcardiograms drawn by this method resemble those produced by elaborate electronic methods. The loops, which fall into a well-defined range in position, shape and time relations, have been described.

We are indebted to Dr. J. P. D. Mounsey for help and criticism.

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A NEW ANGIOCARDIOGRAPHIC SIGN OF PATENT DUCTUS ARTERIOSUS

BY

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It is generally agreed that the clinical diagnosis of patent ductus arteriosus, although easy in many cases, may be very difficult indeed, particularly in such cases where the typical continuous (fistulous) machinery murmur and the thrill over the pulmonic area are not present. As the diagnosis of patent ductus arteriosus carries with it the practical implication of surgical intervention and as the latter today is a relatively safe and easy procedure, it is important to establish the diagnosis beyond reasonable doubt. Any new sign, therefore, that may help in the positive diagnosis of this abnormality is of interest. The ductus itself is rarely visualized during angiocardiography and the angiocardiographic diagnosis of patent ductus depends entirely on indirect evidence, such as: (1) dilatation of the main or left pulmonary artery; (2) elevation of the main or the left pulmonary artery towards the " isthmus of the aorta "; (3) re-opacification of the pulmonary artery from the aorta; (4) persistance of the dye in the pulmonary artery until such time as the left heart is filled as well; (5) localized dilatation of the descending aorta just beyond the isthmus, and (6) left ventricular dilatation (Steinberg *et al.*, 1943; Donovan *et. al.*, 1943; Chavez *et al.*, 1947; Keele, 1948; Dotter and Steinberg, 1949).

Needles to say, all these signs are not present in all cases. According to Donovan *et. al.*, 31 out of 50 proved cases of patent ductus arteriosus have had dilatation of the pulmonary artery, and in 25 per cent of the cases investigated by Steinberg *et al.* the dilatation of the pulmonary artery was absent; 26 of their 27 cases showed the dilatation of the aorta described above, which thus, appears to be a more constant feature. However, we have had difficulty in demonstrating this sign in our cases. The re-opacification of the pulmonary artery as the diodone passes through the aorta may also be difficult to see, as the diodone is often too diluted at this stage and on mixing with the blood in the pulmonary artery it may be practically invisible. This is particularly the case if the ductus is a narrow channel.

The direction of the blood flow in a patent ductus is, with very rare exceptions, from the aorta to the pulmonary artery. This has been proved at operations and by cardiac catheterization. Eppinger and Burwell (1941) have calculated that the volume of blood shunted from the aorta to the pulmonary artery in three of their cases measured between 45 and 77 per cent of the stroke volume of the left ventricle. It is by this " injection " of blood into the pulmonary artery from the aorta that the sign to be described is produced.

The sign consists of a defect in the outline of the main pulmonary artery and is seen at a time when the contrast medium is passing through the pulmonary artery, that is, two to three seconds after the injection of the diodone. As the blood from the aorta does not contain any diodone at that time, the admixture of blood from the aorta via the patent ductus with the blood in the pulmonary artery containing the diodone shows up on the film as a filling defect. This defect is clearly seen in Fig. 1 and 2, and has been seen by us in the last four consecutive cases of patent ductus arteriosus.

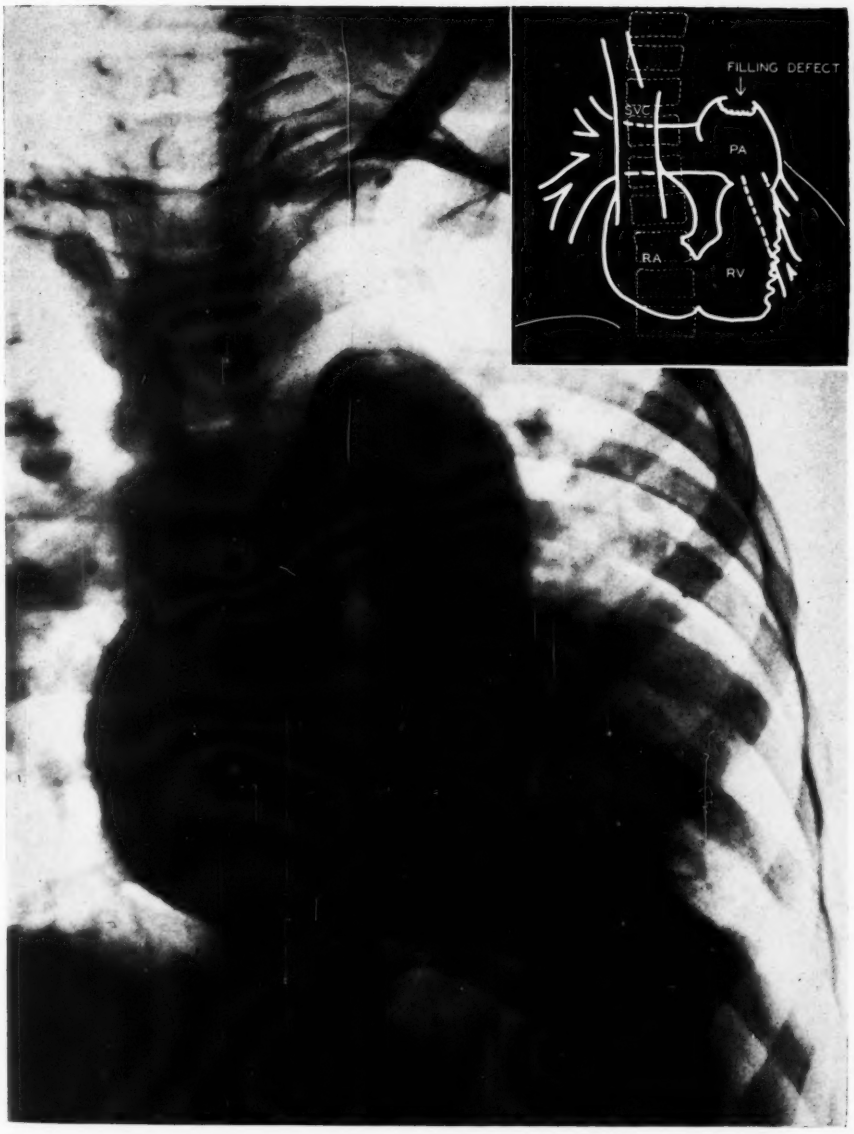

FIG. 1.—Antero-posterior view at 3 sec., showing outline of right auricle, ventricle, and pulmonary artery. Note the defect in the filling of the pulmonary artery. Proved case of patent ductus arteriosus.

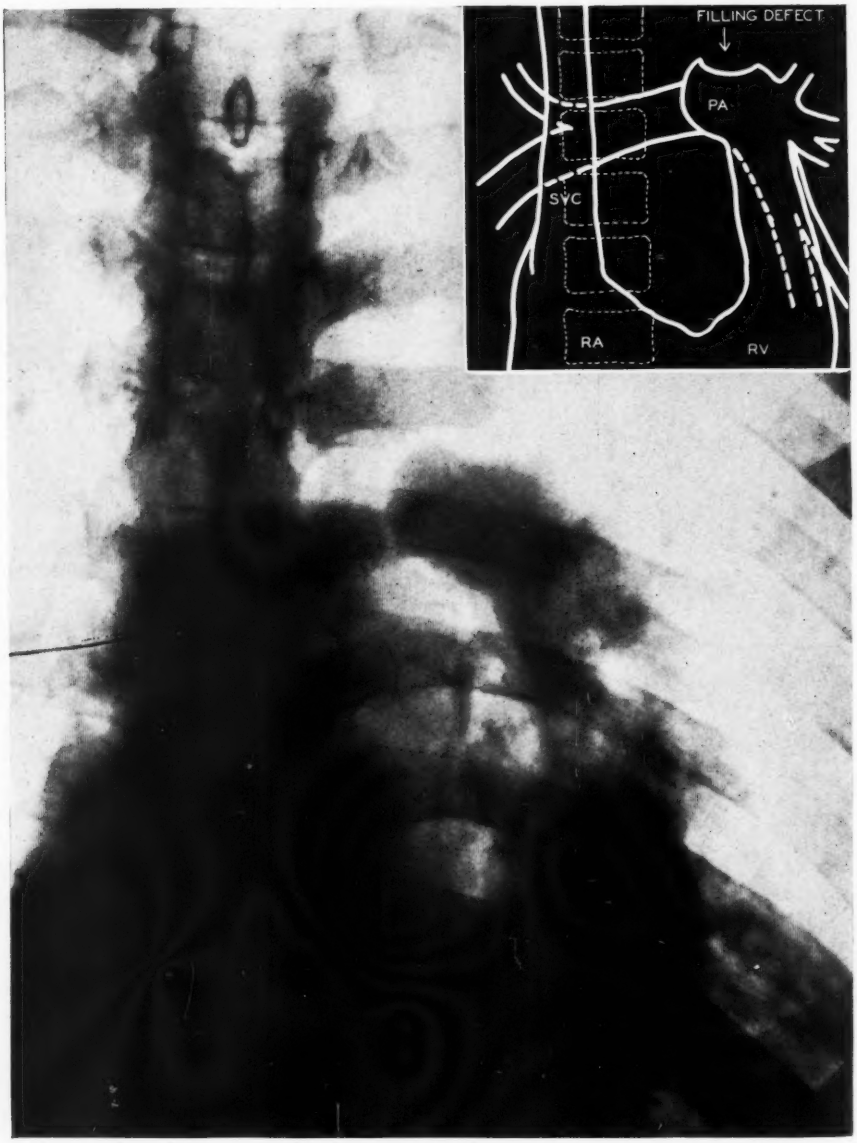

FIG. 2.—Antero-posterior view taken at 2 sec., showing clearly superior vena cava, right auricle, right ventricle, and main pulmonary artery filled. The defective filling in the elevated and dilated main pulmonary artery is clearly seen.

FIG. 3.—Antero-posterior view taken at 3 sec. to show dilated main pulmonary artery in a case of infundibular stenosis. Note the clear outline of the main pulmonary artery.

Two of these were subjected to operation when the diagnosis was confirmed.* The dilatation and elevation of the pulmonary artery as first observed by Steinberg *et al.* is also clearly seen in Fig. 1.

The filling defect, although usually seen in both views, may be more definite in the left anterior oblique position. It may not be present on all plates in which the pulmonary artery is filled,

* These cases were operated on by Mr. Walter Phillips.

presumably depending on the phase of the cardiac cycle at which the plate was taken. It is therefore advisable to take more than one exposure during the time at which the diodone is passing through the pulmonary artery. In our experience, the visualization of this filling defect may be of considerable importance in making a positive diagnosis of patent ductus arteriosus in such cases where the opening is rather small and where consequently, both the dilatation of the pulmonary artery and the re-opacification of the pulmonary artery are absent. Fig. 3 is reproduced to show a marked dilatation of the main pulmonary artery in a case other than patent ductus, and was obtained in a case of infundibular stenosis with some post-stenotic dilatation. The sharp outline of the pulmonary artery in this case is clearly seen and contrasts well with the defect in the two cases with patent ductus arteriosus.

Summary

A new sign in the angiocardiographic diagnosis of patent ductus arteriosus is demonstrated. It consists of a defect in the homogeneous filling with the opaque material of the main pulmonary artery. It is brought about by the injection of blood from the aorta through the ductus diluting the opaque medium as it passes through the pulmonary artery.

I am most grateful to my colleagues in the Department of Medicine, Prof. F. Forman, Prof. F. Brock, and Dr. S. Michelson for referring the cases used in this study. I am grateful for the assistance received from Dr. A. Katz and the staff of the X-ray Department.

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ACTINOMYCES MURIS ENDOCARDITIS TREATED WITH CHLORAMPHENICOL

BY

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In 1926 interest in the *Actinomyces muris* was first awakened by its recovery from the blood and synovial fluid of patients in an epidemic of a febrile illness with arthritis and morbilliform rash at Haverhill, Massachusetts (Parker and Hudson, 1926; Place and Sutton, 1934). This organism is also the cause of some cases of rat-bite fever, which can often be distinguished clinically from those due to the *S. minus* by the predominant symptom of arthritis, and has been reported as producing endocarditis on five occasions in Australia, New York, Panama and Chicago (Rowntree and Rohan, 1941; McDermott *et al.*, 1945; Wedding, 1947; Priest *et al.*, 1947). It has been known to inhabit the nasopharynx of rats in Great Britain since attention was drawn in 1933 to its presence by a sporadic infection in laboratory animals inoculated with blood from bludgeoned rats at Mill Hill (Strangeways, 1933). There are few reports of its appearance in a pathogenic role in man in this country. These are limited to the occasional case of rat-bite fever, and a single fatal case of endocarditis, in which its identity was in doubt (Stuart-Harris *et al.*, 1935). A case of subacute bacterial endocarditis has recently been observed in which this organism was twice isolated from the blood. Clinical arrest was achieved with chloramphenicol after treatment with penicillin had failed.

A typist, aged 27, was admitted to University College Hospital under our care on July 4, 1949. In 1937 she was treated in hospital for twelve months for rheumatic fever. Some time later she was told that she had mitral stenosis. In 1939 she had a second attack of rheumatic fever which responded well to salicylates; at this time she was found to have mitral stenosis and a water-hammer pulse.

In January, 1948, she handled a dead rat which her dog had caught. In February, 1948, she sustained a brief febrile illness, and on March 24 became ill with fever, sweating, fatigue, and pains in hands and knees; a severe pain developed in the left upper quadrant of the abdomen. Pain appeared later in the left side of the chest posteriorly and a diagnosis of pleurisy was made, for which she was admitted to the North Middlesex Hospital on April 2. At this time the temperature was 102° F with rapid pulse and respirations and indeterminate signs at the left base. There was tenderness and pain on movement at the metacarpophalangeal and knee joints. There was considerable cardiac enlargement with mitral stenosis and aortic regurgitation. She was treated with salicylates in full doses but the temperature did not settle for two weeks and her joint pains continued. Early in May the temperature rose sharply and continued for three weeks at a level of about 103° F. A single blood culture was sterile. She began a 28-day course of penicillin, 125,000 units 3-hourly on May 25, and the temperature subsided on May 29. During the course of penicillin numbers of rheumatic nodules appeared on the wrists and elbows and were present for two months. Recovery was slow, and joint pains continued despite salicylates. She left hospital on September 24 and by November 25 was back at work. During this illness the spleen was not palpable and there were no emboli into the skin.

She remained quite well apart from dyspnœa on unusual exertion, until June, 1949, when she developed recurrent pain in the tips of fingers and toes lasting 48 hours at a time, and accompanied by swelling and tenderness of the pulps and bruising under the nails. She also had painful red swellings on the palms and right shin, and became increasingly tired and short of breath.

Temperature was 99° F, pulse 84 and regular, respirations 28, and blood pressure 150/50. She was a plump, cheerful girl, not acutely ill. No cyanosis. No clubbing. No pyorrhœa or pharyngitis. There was forceful arterial pulsation in the neck, and obvious capillary pulsation in the nail beds. The heart was enlarged 16 cm. to the left in the fifth space. There were signs of mitral stenosis and free aortic regurgitation but not of congestive failure. All peripheral arteries were pulsating. The spleen was palpable 2·5 cm. below left costal margin. All joints were normal. There was a red tender swelling 7·5 cm. in diameter on the right shin.

Blood examination showed Hb 74 per cent and 4,600,000 red cells per cu. mm.; white cells 5,600 per cu. mm., with normal differential. E.S.R. 30 mm. in one hour. Urine contained a faint trace of albumen and one red cell per high-power field. Two blood cultures taken in the first few days after admission yielded *Actinomyces muris*. During the first week after admission numerous embolic manifestations were seen, including splinter hæmorrhages under the nails, Osler's nodes in the pulps of fingers and toes, and small spots on the palms of the hands. Pending sensitivity tests, penicillin therapy was begun on July 11 with 600,000 units of procaine penicillin twice daily, giving a level immediately before injection of 0·32 units per ml.

During the first fortnight of penicillin treatment, the temperature partially settled, but embolic phenomena continued and she remained tired and unwell. On July 26 she had a sudden pain in the left upper quadrant of the abdomen and in the left shoulder, and the spleen, which had previously receded, became palpable again and tender. Meanwhile, sensitivity tests had shown that the actinomyces was resistant to penicillin but was of the same order of sensitivity to chloramphenicol as Klebsiella 41. Penicillin was therefore stopped on August 3. Blood cultures on the 5th and 8th of this month were sterile, but continuing embolism showed that the disease was still active. Chloramphenicol 1g. was given on August 10 and followed by 0·5g. four-hourly for the next 28 days. By the end of the first week's treatment emboli had ceased and the general health was much improved.

The patient's convalescence was interrupted by a sudden bout of severe precordial pain and tachycardia; there was no fever, but electrocardiographic evidence suggested a small posterior cardiac infarct. At this point there was no other sign of embolism and she felt well as soon as the pain had subsided. She was discharged to a convalescent home on October 25 after a further six weeks' rest, the blood count showing Hb 100 per cent and E.S.R. 8 mm. in one hour.

Bacteriological Note. Blood cultures were made in "liquoid" (sodium polyanethol sulphonate) broth and incubated in air, air plus 5–10 per cent CO_2, and anærobically plus about 5 per cent CO_2 (von Haebler and Miles, 1938). The first sample of blood was taken on the day of admission, the second two days later. All cultures, ærobic and anærobic, from these two samples yielded an organism having the following characteristics.

Microscopic appearance. Very pleomorphic, irregularly staining, but mainly Gram negative strepto bacillus. A few branching forms seen in liquid culture, numerous serpent and some club forms, no moniliform bodies (Fig. 1, 2, and 3).

Cultural characteristics. The organism was a facultative ærobe and preferred an anærobic atmosphere with CO_2 added. All subsequent cultures were incubated under these conditions. Although growth occurred in the original ærobic cultures it was relatively feeble and subcultures from them were sterile unless CO_2 was added to the atmosphere. In spite of a profuse growth of fluffy colonies in the original anærobic blood liquoid broth, great difficulty was experienced in making successful subcultures and no medium was found which would yield a comparable growth. Subculture on 10 per cent defibrinated human blood agar gave minute non-hæmolytic translucent colonies after 2–4 days, which on further incubation increased to a maximum of about 0·3 mm. diameter. Moderate, slightly granular growth appeared after three days when these colonies were seeded into 30 per cent human serum broth. Cultures in the following media were sterile after five

FIG. 1.—Culture from original blood liquoid broth. Gram stain, × 850.

FIG. 2.—Culture from human blood agar. Leishmann stain, × 850.

FIG. 3.—Culture from Fildes agar. Dark ground illumination, × 600.

day's incubation: 10 per cent oxalated horse blood agar (several cultures were made but only one batch of blood was used); 1 per cent glucose nutrient agar; 5 per cent and 15 per cent horse serum broth; Robertson's cooked meat broth; horse blood broth; 1 per cent glucose broth and human blood agar incubated at room temperature.

Sensitivity tests. These were made on human blood agar. For penicillin and streptomycin, filter paper discs impregnated with standard amounts of the antibiotic were used and for chloramphenicol, which was of unknown strength and unsterile, a hole was bored in the medium and sealed with molten agar. The activity of the antibiotics in discs and "cup" was controlled by seeding the unknown strain on one-half of the plate and a control strain of known sensitivity on the other, the antibiotic lying between them. The results are shown in Table I.

TABLE I

RESULTS OF SENSITIVITY TESTS

	Zone radius	Control zone radius
Penicillin	Nil	15 mm. (Oxford Staph.)
Streptomycin	Growth irregular, result not readable	12 mm. (Oxford Staph.)
Chloramphenicol	17 mm.	17 mm. Klebsiella

Since the controls grew more rapidly than the test strain a comparison of the inhibition zones can only give a very rough estimate of the sensitivity. A more precise test in liquid culture could not be made because no liquid medium was found that could be relied on to yield good growth in a series of tubes. As urgent investigations were now complete the culture was freeze dried and put aside for further investigation. Unfortunately, when it was examined a month later it was no longer viable.

Before changing to chloramphenicol treatment the blood was again cultured in an attempt to demonstrate continued infection in spite of penicillin. Three blood samples, 5 ml. each, were taken on the same day and delivered as before into "liquoid" broth. All three bottles were

incubated in the most favourable atmosphere (anærobic plus CO_2); this was repeated three days later. All six bottles were subcultured thrice weekly and all remained sterile after four weeks' incubation.

Although the investigation of the strain could not be completed, it is clear that it resembles *Actinomyces muris* more closely than any other organism previously isolated from human blood. It is of interest that so delicate an organism flourished in the primary human blood—"liquoid" broth cultures.

Discussion

It seems probable that the original infection with *Actinomyces muris* occurred in 1948, a few weeks after contact with a rat in January. Though blood culture was negative, it is difficult to escape from a diagnosis of subacute bacterial endocarditis at this time in view of the splenic pain and the prompt response to penicillin of the fever which had resisted salicylates. It is also probable, however, that there was some active rheumatism at the same time in view of the rheumatic nodules.

In previous cases of subacute bacterial endocarditis from whom *Actinomyces muris* has been recovered, the organism has been sensitive to penicillin (McDermott *et al.*, 1945; Priest *et al.*, 1947). The response of the fever in 1948 to penicillin suggests that *Actinomyces muris* may have been present then in the blood and had become resistant to penicillin by the time it was isolated during the illness of 1949. When dealing with an organism of this sort it is not unusual to encounter difficulties in culture. This is particularly well shown by Rowntree's (1941) case, when the disease ran a fulminant course, but the actinomyces was not recovered till necropsy, and by the two negative cultures in this case at a time when signs of active infection were present.

Occasional cases of subacute bacterial endocarditis from whose blood various strains of actinomyces have been recovered are on record (Curtis *et al.*, 1944; MacNeal *et al.*, 1946; Beamer *et al.*, 1945), but there appear to be only six instances in which *Actinomyces muris* is involved and these are shown in the accompanying Table II. All the previously recorded cases have been fatal, though one showed temporary improvement with penicillin. One of the interesting features of the case recorded here is the comparatively benign clinical course. The fulminating course of the endocarditis in the case described following a rat-bite (Rowntree, 1941) is comparable in its severity

TABLE II

Records of *Actinomyces Muris* Endocarditis

Case	Course	Blood culture	Mode of infection	Treatment	Outcome
Stuart-Harris *et al.*, 1935	Subacute	Not known	Not known	Nil	Death
Rowntree *et al.*, 1941	Acute	Negative but *Actinomyces muris* recovered from heart valve at autopsy	Bitten by rat	Nil	Death
McDermott *et al.*, 1945	Subacute	Positive	Contact with rats	Penicillin	Temporary clinical improvement but death in cardiac failure
Priest *et al.*, 1947	Subacute	Positive	Not known	Penicillin	Death
Wedding, 1947	Subacute	Negative but actinomyces recovered from heart valve at autopsy	Not known	Sulphonamides	Death
Wedding, 1947	Not known	No blood culture but actinomyces recovered from heart valve at autopsy	Not known	Nil	Death
Stokes *et al.*, 1949	Subacute	Positive	Contact with rats	Chloramphenicol	Recovery

to rat-bite fever. In contrast, the course run by the subacute cases is more like that of Haverhill fever; in this disease the organism is not injected directly into the blood stream and the route of entry is uncertain.

There were no clinical features that distinguished this case from instances of subacute bacterial endocarditis caused by other organisms. It is noteworthy that 65 g. of chloramphenicol were given over a period of 28 days with no toxic symptoms other than occasional slight headache; weekly white cell counts during this time showed no fall in granulocytes.

Summary

A case of subacute infective endocarditis due to *Actinomyces muris* is described.

There was a satisfactory response to chloramphenicol which controlled the infection after penicillin therapy had failed.

No toxic effects resulted from giving 65 g. of chloramphenicol in 28 days.

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Maurice Cassidy.

MAURICE CASSIDY

Maurice Alan Cassidy died at his home in London on October 22, 1949, in his seventieth year. He was the eldest son of a doctor, D. M. Cassidy, C.B.E., who was for fifty years medical superintendent of the Lancaster Mental Hospital. After his schooldays at Lancaster, Cassidy went to Clare College, Cambridge, where he was a scholar and obtained first-class honours in both parts of the Natural Science Tripos. He then entered St. Thomas' Hospital, with which he was closely associated for the rest of his life. He showed great ability as a student, and after qualifying in 1905 he held there several resident posts, including that of Resident Assistant Physician for two years; in addition, he was a demonstrator of physiology and medical registrar.

About this time, Cassidy had thoughts of following an academic career and he was offered a Fellowship of his Cambridge College, but he decided to remain in London. He was elected F.R.C.P. in 1913 and in the same year he joined the honorary staff of St. Thomas' Hospital. In 1914 he was Goulstonian lecturer at the College of Physicians. During the 1914–18 war Cassidy spent two years in the army, partly in France, where he was physician to an Anglo-Belgian hospital at Calais. In 1916, however, he had the misfortune to contract pulmonary tuberculosis, which led to his being invalided from the army, and he did not return to full work for two years. Those who knew him well at this time speak of the courage and determination with which he bore and overcame his disability.

In addition to his work at St. Thomas', Cassidy was for many years chief medical officer to the Metropolitan Police and on retiring from this post in 1929 he was awarded the C.B. He was also for many years consulting physician to Lord Mayor Treloar's Cripples Hospital at Alton, to King Edward VII Sanatorium at Midhurst, and to the Children's Heart Hospital at West Wickham. He retired from the active staff of St. Thomas' just before the 1939–45 war, but within a month of its outbreak he was back again at active work and there gave much of his time both in the wards and in the outpatient department until he finally retired late in 1945.

Many other honours came to Cassidy. At the Royal College of Physicians he successively held the offices of Councillor, Censor, and Senior Censor, and in 1946 he was appointed Harveian Orator. In 1946–48 he was President of the Royal Society of Medicine, and in 1949 he was elected an honorary fellow of his old college at Cambridge—an honour that gave him great pleasure.

Cassidy's name was familiar to a wide circle outside the profession owing to his long connection with the Royal Household. In 1930 he was appointed Physician to the Household, and in 1932 Physician in Ordinary to King George V and then Physician in Ordinary to King George VI. During this period he had grave responsibilities which he met with characteristic courage and wisdom. He was created K.C.V.O. in 1934 and shortly before Cassidy's death His Majesty conferred upon him the signal honour of visiting him in his home and investing him with the G.C.V.O.

Cassidy became interested in cardiology early in his career. In 1913 he studied under Thomas Lewis at University College Hospital, where he met most of those who are now the older generation of London cardiologists. Lewis chiefly taught us how to use the polygraph and the Cambridge Einthoven string galvanometer, the reading of the tracings, and the mode of production of the various arrhythmias. This early interest in cardiology grew with the years, but by no means to the exclusion of his interest in general medicine. Cassidy was elected a member of the Cardiac Club in 1926. He introduced a discussion on vasomotor angina at the Leeds meeting in 1934 and he was chairman at the London meeting in 1935. He was also chairman of the British Cardiac Society meeting at St. Thomas' Hospital in 1943. He wrote several papers of clinical cardiological interest

and for his Harveian Oration he chose the subject of coronary disease, of which he had exceptional experience.

Maurice Cassidy was an outstanding physician of his time. His greatness lay in a blend of attributes of character with professional skill. Success never affected him adversely, and his ambition seemed to be to serve and satisfy the needs of his patients who quickly perceived his skill and his sympathy.

Sir Charles Max Page writes, " I was associated with Maurice Cassidy in work and play since he came up to St. Thomas's in 1902 and I should like to add a short note. Though Cassidy's professional standing was based on his interest in cardiology, he remains in my memory as a general physician gifted with a singular intuitive ability in diagnosis and possessed of a very human sympathy. His sense of humour and interest in the foibles of humanity lightened his attitude to his work and I think assisted him in gaining the confidence and devotion of his patients. His cheerfulness and courage in withstanding and overcoming the ill-health that threatened his future on more than one occasion gave some measure of the strength of his character.

" He had developed the ability to concentrate on the current task to an enviable degree. When in London he took little time off his professional work; on holiday whether fishing or deer-stalking he displayed amazing energy and stamina.

" His death has deprived London of a fine physician and stolen from many of us a loveable companion."

Cassidy married in 1918, Elsie, daughter of Frederick Relfe, and she proved an ideal companion and a gracious hostess. There were no children. Somewhat shy by nature, he was a man of high courage and integrity; he loved his fellow men, so that his abounding kindness and human understanding not only benefited his patients but were always at the disposal of the many who sought his help and guidance. As a physician he possessed a wide knowledge of medicine which he applied with a clear mind, common sense, and wisdom. The union of these qualities made him the ideal physician to innumerable patients, students and nurses, his colleagues and friends.

ARNOLD STOTT

A. G. GIBSON

Alexander George Gibson, who died at Oxford on January 11, 1950, aged 74, was a prominent member of the Cardiac Club. He was chairman of the meeting at Oxford in April, 1922, when it was decided that the club should be founded: John Cowan was the first secretary and Gibson followed him, serving from 1925 to 1928. He was also chairman of the committee of the Cardiac Society that decided in 1937–38 the time had come to start the British Heart Journal. It is, therefore, particularly fitting that some short record of his life should appear in these pages.

Born at Hull in 1875, Gibson was educated at University College, Aberystwyth, where he read agriculture, and afterwards at Christ Church, Oxford, and at St. Thomas' Hospital, where he held a house appointment. After graduating B.M., he became house-physician to the Radcliffe Infirmary and County Hospital in 1904, and his long association with Oxford remained unbroken from then

on. He held many posts at the Radcliffe, and helped to raise it to the eminent position that it now holds.

When in 1904 Gibson settled in Oxford he was brought into contact with James Ritchie, reader and later professor of pathology, and with Burdon Sanderson, the regius professor of medicine, whom Osler succeeded the following year. His association with Osler was a particularly happy one, and over the years until Osler's death in 1919 he acquired a certain number of mannerisms from the regius professor, whom, incidentally, he attended in his last illness. It was during these years that he built up his reputation as a pathologist and particularly as a demonstrator of morbid anatomy in the post-mortem room. In 1905 he obtained the M.R.C.P. and in 1908 his D.M: he was elected F.R.C.P. in 1913.

In the early days at Oxford, Gibson had a small general practice in addition to being engaged on pathological teaching and research as University demonstrator at the Museum and as Pathologist to the Radcliffe Infirmary. Later he embarked on consultant practice, becoming particularly interested in cardiology. Both as a family physician and as a consultant, he had the power of

applying his knowledge with practical success, and his kindness and patience endeared him to his patients. He was quiet and confident in manner and anxiety began to be allayed as soon as he entered the sick-room.

Gibson was appointed physician to the Radcliffe Infirmary in 1919, and was on several occasions Litchfield Lecturer in Medicine and later Nuffield Reader in Pathology. In 1928 he delivered the Bradshaw lecture on pyelitis and pyelonephritis. From 1931 to 1943 he was, in turn, councillor and examiner and censor at the Royal College of Physicians.

There can be few Oxford men who graduated between 1910 and the recent world war who do not owe a great deal to him. He was a good teacher, combining a profound knowledge that ranged widely over clinical and pathological medicine with a clear power of exposition and enthusiasm for seeing that his students understood what he was talking about. His demonstrations of morbid anatomy will be recalled with pleasure by many generations of Oxford men. Clarity of expression was one thing that made them outstanding, and also his careful and accurate correlation of the clinical and post-mortem findings, based on his broad knowledge of these subjects. Though always popular and fond of his students, he was a disciplinarian who knew how to command attention.

He wrote several books. *The Radcliffe Infirmary*, published in 1926, is a very complete account and is written with affectionate regard for the hospital, its benefactors, and its staff. In 1927 he collaborated with Dr. W. T. Collier in *Methods of Clinical Diagnosis*, an excellent guide to the subject. In 1930 came *The Mycoses of the Spleen;* Gibson thought at one time that he had discovered the causative organism of splenic anæmia but this work was not substantiated. Finally, in 1933, a comprehensive series of essays, *The Physician's Art:* this is perhaps less easy reading than Osler's *Counsels and Ideals* but few doctors could fail to benefit from its wisdom and common sense, and it shows the high ideals that Gibson set before himself and succeeded in reaching.

Gibson's best known paper, written while he was still young, is his original description of the third heart sound (*Lancet*, 1907, **2,** 1380). Orias and Braun Menedez, in *The Heart Sounds in Normal and Pathological Conditions* (1939) write as follows:

" The third sound was first described in 1907 by Gibson, whose only means of exploration was simple auscultation. To this author is due not only the credit of its discovery but the much greater merit of having cleanly stated its physiological character and its principal attributes, at a time when the means for observation and study of the heart-sounds were so limited. Referring to his discovery, Gibson wrote: ' The sound is by no means easy to hear . . . nor is it possible to hear the sound at every systole; from my own observations it is best heard in the short interval between expiration and inspiration. The quality of the sound is low pitched and clear, with no suspicion of harshness or anything suggesting a murmur. It is slightly increased in intensity and raised in pitch by pressure on the abdomen.'

" Graphical confirmation of the existence of the third sound was obtained very soon after Gibson's publication. Einthoven (1907), at Gibson's suggestion, went over his collection of phonocardiographic records, and in several of them found vibrations appearing some distance after the second sound, that is at the moment referred to by Gibson."

It is true that Gibson called his paper " A hitherto undescribed wave in the jugular pulse " and that it is doubtful whether the sound and the wave really were simultaneous, but this hardly detracts from the merit of his original observation.

Gibson was a member of the Association of Physicians, of the Cardiac Society, and of the Medical Pilgrim's Club. He was Chairman of the Oxford division of the B.M.A. in 1933, and when the Association met at Oxford in 1936, President of the Section of Medicine. He was also a past president of the Oxford Medical Society and helped in founding the Oxford Clinical Club, in which all branches of the local medical profession were represented—general practitioners, research workers, consultants, and specialists in all branches: the fortnightly meetings at 27 Banbury Road were a source of help to all the members and owed much to Gibson.

Gibson regularly attended the meetings of the Cardiac Society, and many friends, especially his old pupils, counted a further talk with him as one of the pleasures of the meeting. He took part in

many discussions and could be relied upon for his wide knowledge of pathology as applied to the heart—a field that is, perhaps, less well represented among the present members of the Society.

At the 1925 meeting, the discussion on ischæmic necrosis of the heart was opened by Gibson who had collected a good deal of material that helped in the understanding of cardiac infarction, then only recently recognized as a clinical entity that could be diagnosed during life.

Gibson had a long experience of medical journals, as he was the capable and tactful secretary of the editorial board of the *Quarterly Journal of Medicine* from its foundation in 1907 to 1937, and one of its Editors from 1929–37. It was, therefore, natural that when the question of starting the *British Heart Journal* was under consideration, his help and advice were of much assistance to the committee that decided in 1937–38 to start this journal.

The last meeting in which he took part was at Oxford in 1941; he was chairman and helped in many ways to make it a great success; he arranged an interesting exhibition of old medical books from the Merton College Library. When the Society met again at Oxford in 1946 he was, unfortunately, too ill to attend.

In addition to his work and his teaching and writing, Gibson was fond of growing flowers, and when ever possible, spent the Sunday afternoon in his garden. He was interested in many aspects of nature and also in genealogy and was a keen member of the Genealogical Society.

Gibson was never quite the same after the tragic death of his wife in 1942, and for the last five years of his life was confined to bed following a cerebral hæmorrhage. He remained cheerful and serene and was fortunate in the devoted services of his daughter. He leaves two sons also, both members of the medical profession.

MAURICE CAMPBELL

H. J. STARLING

Hubert John Starling died at the age of 76. He was born in India, where his father was Clerk of the Crown in Bombay, and returned to England for his education at St. Paul's School, London. He entered Guy's Hospital in 1891, from which he graduated in 1897 and proceeded M.D. in 1899. Being the youngest son of the family, he was at Guy's several years later than his eldest brother, Ernest H. Starling, the distinguished physiologist.

After holding house appointments at Guy's Hospital, Hubert Starling went as Civil Surgeon with the South African Field Force and served until invalided home with dysentery. He obtained the D.P.H. Cambridge in 1901 and in 1902 settled in general practice in Norwich, which was his home for the rest of his life. Amongst his activities he made a speciality of anæsthetics and was the first honorary anæsthetist to be appointed at the Norfolk and Norwich Hospital in 1911.

He was thus led to work at circulatory problems, which remained his chief medical interest. He recorded his observations on blood pressure with the mercury sphygmomanometer, and then passed

on to the MacKenzie polygraph. Starling was disappointed at being rejected for medical service in the first world war, but on the recommendation of MacKenzie and Lewis he was later appointed to the Military Heart Hospital at Colchester. Here he enjoyed the work and opportunities of making friends with cardiologists in Great Britain and overseas.

After the 1914–18 war he returned to Norwich, gave up his general practice, and became a consulting physician with leanings towards cardiology. He was one of the fifteen original members of the Cardiac Club. In 1926 he opened the discussion on angina pectoris and in 1929 on vaso-vagal attacks. He was appointed a physician to the Norfolk and Norwich Hospital and began a happy period of his life, marred only by fibrositis, attacks of which became more and more of a handicap. On retiring from hospital work, he continued his consulting work and during the second world war was active as Chairman of the Norwich medical board of the Ministry of Labour and National Service and he held this office till last year. Starling was very happy in his home life. He married a daughter of the late Dr. Thomas Fairbank of Windsor, and his wife took an active part with him

in the musical and artistic interests centred in Norwich. Mrs. Starling's vagaries of health provided him with quite a lot of data for his researches and all his new gadgets were tried out on her. She was the willing cooperator, even patient victim, of his early experiments with blood-pressure apparatus, with the polygraph and with the electrocardiograph through the years.

This was the background in which Starling lived and worked, but it is necessary to try to appraise the man as known to his friends and the older members of the Cardiac Club. His early upbringing in the Catholic Apostolic Church and his training at Guy's made him an authoritarian; for him, medicine was an ordered cosmos and he was not attracted by novelties, which took some time for him to assimilate into the order of things. I remember in the early nineteen-twenties reporting on a case he sent for review that there was a calcified pericardium. He wrote back a long pungently expressed letter that it could not be as he had consulted all the textbooks available and none mentioned calcified pericardium. Many years later he himself reported two or three cases of calcification of the pericardium from the Norfolk and Norwich Hospital. But Starling's years in general practice before becoming a consultant made him a sound and broad-minded physician. He remained didactic on ward rounds but mellowed with the years. His papers to the Cardiac Club read at a rapid rate with his slight lisp were sound but dogmatic, and in argument he would explode into his characteristic loud laugh, equally disconcerting whether as approbation or derision. Starling was best in a small group of three or four discussing patients; his case memory was accurate and his illustrations apposite. He liked to record his observations and the list of his publications appended shows the catholicity of his tastes and the breadth of his interests. He remembered with pleasure his association with colleagues at the Military Heart Hospital at Colchester in the first world war.

S. W. PATTERSON

Major Publications

1906 Observation on arterial blood-pressure in heart disease, *Lancet*, **2**, 846.
1910 The value of blood-pressure determinations in toxæmia of pregnancy, *Ibid*, **2**, 784.
1918 Subacute bacterial endocarditis, *Brit. med. J.*, **2**, 154.
1922 Endocarditis lenta, *Quart. J. Med.*, **16**, 263.
1923 Tonsillar and rheumatic infections, *Guy's Hosp. Rep.*, **73**, 388.
1930 Case of megacolon with unusual attacks of tachycardia, *Lancet*, **2**, 1013.
1931 Angina pectoris and coronary occlusion, *Practitioner*, **126**, 652.
1932 Recurrent, subacute necrosis of pancreas, *Guy's Hosp. Rep.*, **82**, 269.
1935 Two cases of achalasia of cardia associated with chronic gastric ulcer, *ibid.*, **85**, 197.
1935 (with Camps, F. E.) Two cases of achalasia with pressure symptoms, *Ibid.*, **85**, 201.
1938 (and others) Two cases of Graves' disease with muscular atrophy, *Ibid.*, **88**, 117.
1939 Syphilis of the lungs, *Quart. J. Med.*, **32**, 381.
1941 (and others) Nature and treatment of effort syndrome, *Proc. Roy. Soc. Med.*, **34**, 541.

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NOTE BY EDITOR

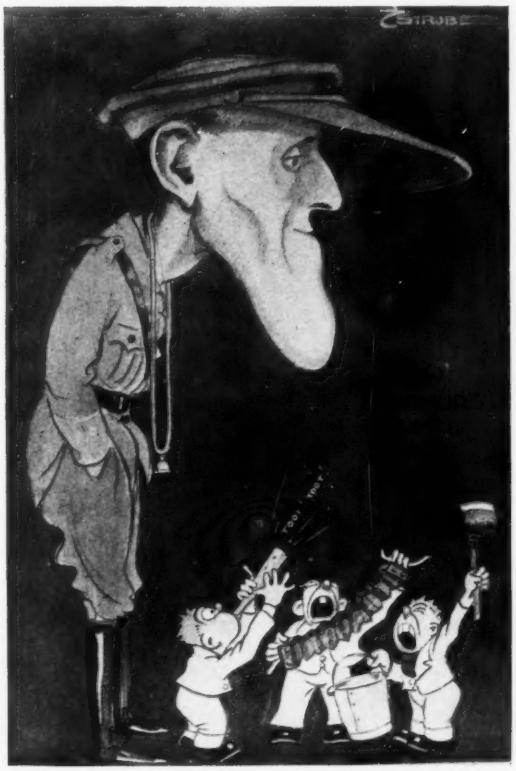
The Cardiac Society is indebted to John Hay for many things, and among them his excellent photographs of the early meetings of the Cardiac Club and its members. In this number it is our sad duty to publish memoirs of three of the senior members of the old club and it is thought that these informal snapshots will be a lively reminder of them.

In the group opposite, Gibson is shown standing on the right with Carey Coombs (centre) and Lewis (on the left), both in singularly characteristic attitudes; this was taken in John Hay's garden at Aigburth about 1928. Perhaps the picture of Gibson inserted in the memoir, taken when he was in a happy mood at one of the meetings, gives a better impression of him as a man.

The photograph of Cassidy (not published) fails to do justice to two of his great qualities, his friendly charm and his singularly unruffled demeanour in all circumstances, and Lady Cassidy adds that few photographs of him seemed good and has chosen a chalk drawing by Mrs. Campbell Dodgson.

In the lower picture opposite, Starling is shown with John Cowan. Except that they look perhaps older than they did at most meetings of the Society, everyone would regard these as characteristic expressions.

Starling was fond of the cartoon of himself which is shown below. It was drawn by Strube when Starling was working at Colchester during the 1914–18 war.



Starling.

ABSTRACTS OF CARDIOLOGY

The Clinical Aspects of Complete Auriculoventricular Heart Block: A Clinical Analysis of 71 Cases. L. W. IDE. *Ann. intern. Med.*, **32**, 510–523, March, 1950.

Patients of any age may have complete heart block (8 intrauterine cases have been reported), but the incidence is much greater in later life. A ratio of 2 or 3 males to 1 female may be related to the frequent association with coronary sclerosis which is found in 50 to 75% of all cases. In the present series of 71 cases 8 were related to acute myocardial infarction, in 12 a digitalis substance was responsible (the block disappearing within an average of 5 days after discontinuing the drug), 9 were congenital in origin, 4 were related to rheumatic fever, 2 to scarlet fever, and 1 to syphilis. Diphtheria, hyperthyroidism, neoplasm affecting the conducting system, uræmia, pneumonia, peritonitis, and trauma have all been mentioned as ætiological factors.

Symptoms, when present, vary from transient episodes of mild giddiness to frequent attacks of syncope and convulsion. Stokes–Adams attacks of loss of consciousness are due to ventricular standstill, ventricular tachycardia, ventricular fibrillation, or to a combination of these. Only 25 patients of this series had any symptoms due to the heart block. The average ventricular rate was 45. Rapid rates may be due to myocardial infarction or congestive failure. Prognosis depends upon the severity of the symptoms and upon the associated heart disease. Patients with congenital defect live longer.

It is necessary to treat complete heart block only when there are associated symptoms or when it is the result of drug intoxication. In some instances it can be ignored and therapy directed at other manifestations of heart disease. "Paredrine," ephedrine, adrenaline, and quinidine have been used in the treatment and prevention of Stokes–Adams seizures.

[The article includes an excellent historical review of the subject.] *T. Semple*

An Attempt at Treatment of Cardiac Decompensation by Ligation of the Inferior Vena Cava. F. D'ALLAINES, H. DE BALSAC, C. DUBOST, —. SCEBAT, —. FRILEUX, and —. ALLARY. *Mém. Acad. Chir.*, Paris, **75**, 791–799, Nov. 30, 1949. 3 figs., 13 refs.

Functional inadequacy of the left side of the heart leads to pulmonary hypertension, which is followed in turn by right-sided heart failure with liver enlargement, failure of excretion of salt and water, and increasing dropsy. The authors have attempted to alleviate this condition by ligation of the inferior vena cava just below the renal veins, it being hoped in this way to reduce right auricular pressure (observations made in 2 cases showed a fall from 29 to 14 cm. of water in the first and from 35 to 19 cm. of water in the second), and to facilitate venous return from the kidney and liver with a resulting improvement in the output of salt and water. The ligature is intended to protect the right heart from the great volume of blood by which it may be almost swamped when there is a rapid change in position or when the patient is recumbent. Operation is only undertaken when there has been an unsatisfactory response to prolonged medical treatment, and where resumption of even the mildest activity leads to an immediate relapse. Sixteen patients have been subjected to operation so far, 14 with mitral disease and 2 with hypertension. There was one post-operative death. The vessel is approached by the extraperitoneal route through a pararectal incision under local analgesia (paravertebral and splanchnic block). Phlebitis, despite energetic prophylactic treatment with heparin, is the bugbear of the convalescent period. The immediate result is very pleasing, with quite dramatic relief of orthopnœa and the distressing paroxysms of nocturnal dyspnœa. None of the patients has so far been followed for more than 6 months and it is too early to say what the late results will be.

M. R. Ewing

Technique of Transthoracic Block of the Cardioaortic Plexus in Angina Pectoris. J. J. DZHANELIDZE. *Khirurgiya*, No. 1, 10–14, Jan., 1950.

After infiltration of a wide area over the manubrium sterni a transverse incision is made down to periosteum. In the centre of the manubrium the compact and superficial layers of cancellous bone are chiselled away, then with a drill 1½ cm. in diameter a hole perforating the manubrium is made. Through its centre a fine needle is pushed and, when it reaches the aorta, warm 1% solution of procaine is slowly injected. The author claims disappearance of anginal attacks in 16 out of 27 patients treated in this way. *Z. W. Skomorokh*

Transfusion Treatment of Shock due to Myocardial Infarction. F. H. EPSTEIN and A. S. RELMAN. *New Engl. J. Med.*, **241**, 889–893, Dec. 8, 1949.

Clinical observations are reported on 50 patients in "shock" following coronary occlusion; 20 of these received a transfusion. The criteria of shock are a systolic blood pressure remaining below 90 mm. Hg. for at least one hour associated with weakness or stupor, cyanosis, and coldness and dampness of the skin. For transfusion, an average of 700 ml. blood or plasma was usually given at the rate of 250 ml. an hour, starting 3 to 4 hours after the appearance of shock. The

authors conclude that, although transfusion seemed to be of benefit in a few cases, there was no significant difference between the two groups as regards mortality and recovery from shock. Transfusion did not seem to increase the incidence of pulmonary œdema or the severity of congestive failure. *R. T. Grant*

Propylthiouracil in the Treatment of Angina Pectoris: A Comparison with Thiouracil Therapy. S. BEN-ASHER. *Ann. intern. Med.*, **32**, 528–541, March, 1950.

Propylthiouracil is not as effective as thiouracil in the treatment of angina pectoris. The effect of the former drug on the basal metabolic rate and blood cholesterol level is considerably less than that of thiouracil, but toxic effects occur less frequently. *T. Semple*

Tetraethylammonium Chloride in the Treatment of Angina Pectoris. W. J. ATKINSON. *Amer. Heart J.*, **39**, 336–352, March, 1950.

Intravenous injections of tetraethylammonium chloride (TEAC) were given to 28 patients with angina of effort at intervals which varied from twice a week to once a fortnight over a period ranging from 1 to 20 months. A sufficient dose was given to cause pronounced tingling in the feet, the optimum quantity being determined separately in each case. All the patients had been treated for some months with phenobarbitone, nitroglycerin, or digitalis, and their cardiac condition had become stabilized. In 25 cases there was an improvement, as judged by the frequency of attacks or the amount of exercise needed to precipitate an attack, during treatment with TEAC. *D. Verel*

Cholesterol Content of the Coronary Arteries and Blood in Acute Coronary Artery Thrombosis. L. M. MORRISON, and K. D. JOHNSON. *Amer. Heart J.*, **39**, 31–34, Jan., 1950.

The authors suggest that a disturbance in lipid metabolism is a factor in the pathogenesis of atherosclerosis. This suggestion is based on the following findings. (1) The average cholesterol content of the coronary arteries in a group of patients who died from an acute coronary artery thrombosis was four times as great as the average cholesterol content of the coronary arteries in a comparable control group. (2) Hypercholesterolæmia was found in most of the patients who died of coronary thrombosis, as compared with the average blood cholesterol level in the control group. *R. T. Grant*

Vitamin E in Intermittent Claudication. A. H. RATCLIFFE. *Lancet*, **2**, 1128–1130, Dec. 17, 1949.

In the neurovascular clinic at Manchester Royal Infirmary vitamin E was employed in the treatment of 41 patients suffering from intermittent claudication associated with obliterative vascular disease of the legs. The treatment was applied to cases conforming to certain data obtained from walking tests. Each patient carried out the exercise of walking either along the hospital corridors or on a platform with a moving conveyor belt. At the moment when pain was first experienced a note was made of the distance traversed by the patient. A second measurement of the distance was made when the patient stopped walking. The cases selected for treatment were those in which the halting distance did not exceed 500 yards (450 m.), and the pain, though persistent, was not of increased intensity after the onset of claudication. None of these patients had received any other form of treatment, nor were they regarded as suitable for sympathectomy.

Vitamin E was prescribed in the form of "ephynal," a synthetic preparation of α-tocopherol. The dose was 400 mg. daily by mouth. Walking tests were repeated after 3 months' therapy. Improvement was considered to have taken place when the patients were able to walk 880 yards in comparative comfort and without experiencing pain. The tests revealed that 34 patients had improved, although beneficial effects were not observed until the treatment had been given for periods ranging from 4 to 8 weeks. On the other hand, only 5 of 25 controls showed a similar degree of improvement.

Reference to mathematical tables for experimental data involving small numbers showed that these figures can be assessed as "highly significant." Thus vitamin E is indicated in the treatment of claudication, but it is effective only when administered daily in large doses and for at least 3 months. *A. Garland*

The Cardiovascular System in Toxæmias of Pregnancy. A. B. BENCHIMOL and R. D. CARNEIRO. *Arch. brasil. Cardiol.*, **2**, 397–416, Dec., 1949.

The authors think that, whereas the hypertension accompanying pregnancy toxæmia has been extensively studied, the myocardial changes have not. The authors maintain that 50% of hypertensive women who become pregnant develop toxæmia whereas the condition only arises in 2% of normal subjects. They also consider that the duration of the toxæmia is more important than its degree in bringing about permanent hypertension.

Cardiac asthma and acute pulmonary œdema occur in pregnancy toxæmia; the heart may become acutely dilated and later return to its normal size. They quote Dexter and White who believe that heart failure is due primarily to the "load" of the hypertension; the modern view, however, seems to be that there is primary myocardial damage as shown by post-mortem and electrocardiographic changes which vary considerably.

Paul B. Woolley

The Effect of Lumbo-Dorsal Sympathectomy and Splanchnic Resection in Hypertension. A Preliminary Report on 18 Carefully Selected Cases Followed for 3–13 Years After Operation. A. C. ABBOTT. *Manitoba med. Rev.*, **29**, 567–571, Nov., 1949.

The author reviews very conservatively the results of operation in 18 cases of arterial hypertension—5 treated by the technique of subdiaphragmatic splanchnic resection and sympathectomy described by Adson and Craig, and the remainder by the combined supra- and infra-diaphragmatic procedure of Smithwick. The

patients are separated into three age-groups: (1) 18 to 30 years (5 patients followed up 6 to 13 years); (2) 31 to 40 years (7 patients followed up 3 to 9 years), and (3) 41 to 60 years (6 patients followed up 4 to 8 years) and the blood-pressure response and symptomatic improvement in each group tabulated. Each case is briefly described. Three patients have died, 6 months, 7 years, and 7 years respectively after operation. In the remainder, the symptomatic results (which correspond usually, but not always, with the results as judged by fall in blood pressure) are given as follows: group (1) good in 2 cases, fair in 3; group (2) good in 3 cases, fair in 2 (2 deaths); group (3) good in 3 cases, fair in 2 (1 death). The author concludes that operation offers relief which no other treatment can provide at present.

D. W. C. Northfield

The Effect of a War-imposed Protein Free Diet on the Blood Pressure Level in Essential Hypertension. J. KOHÁRI-KUCHÁRIK. *Amer. J. med. Sci.*, **219**, 27–29, Jan., 1950.

Almost complete protein-starvation during the 10 months following the siege of Budapest in 1945 was found to have had no effect on the blood pressure of 39 patients with essential hypertension observed by the author throughout this period.

G. Schoenewald

Renal Venous Pressure in Chronic Congestive Heart Failure. M. H. MAXWELL, E. S. BREED, and I. L. SCHWARTZ. *J. clin. Invest.*, **29**, 342–348, March, 1950.

The pressure in the renal vein, measured by catheterization, under fluoroscopic control, from the antecubital vein in 10 cases of congestive heart failure was approximately double that in 17 normal controls. Calculation of the renal vascular resistance suggests that renal vasomotor changes are largely responsible for the decrease in renal plasma flow and filtration rate in heart failure.

D. Verel

Myxoma of the Left Auricle. P. M. MCALLEN. *Brit. med. J.*, **1**, 932–934, April 22, 1950.

Arteriography in Raynaud's Disease. M. SERVELLE. *Arch. Mal. Cœur*, **42**, 532–538, May, 1949.

The study of the arteries of the hands by means of arteriography was found useful in 50 cases of Raynaud's disease. In the patients studied some arteriograms were obtained during an induced attack of arterial spasm in the hands. The lateral digital arteries were the only vessels to show radiological abnormalities; those of the thumbs always appeared normal. In 26% of the cases all the digital arteries were patent but some of them appeared thinner than normal. In 62% arterial occlusion was evident in one or more fingers; most commonly the thrombotic occlusion was found to be at the level of the second phalanx. Below the site of occlusion the arteriogram sometimes revealed the presence of a collateral circulation formed by very tiny filiform vessels. In others, the non-thrombosed vessels were of an unusually thin calibre, this being interpreted as being due to arterial spasm. Clinically, the patients with radiological evidence of thrombosis had typical scarring of tips of fingers from dry symmetrical gangrene in the terminal phalanges.

A. I. Suchett-Kaye

Thiocyanate Therapy. W. F. CONNELL, G. K. WHARTON, and C. E. ROBINSON. *Canad. med. Ass. J.*, **62**, 20–27, Jan., 1950. 4 figs., 14 refs.

In the past 20 years over 60 papers have been published on thiocyanate therapy of hypertension, and before 1936, when Barker reported the simple method of estimating sodium thiocyanate in serum, 9 cases of fatal poisoning were reported. It is suggested that the optimum dosage and the selection of suitable patients have not been adequately discussed. In the present study there were 140 persons (50 out-patients from a hypertension clinic, 30 in-patients, 10 healthy interns, and 50 undergraduate medical students).

The drug is indicated in cases of severe headache, and it is a " sovereign remedy " for this symptom. It is not primarily useful for reducing the blood pressure [other authors disagree]. Patients in group I of the Keith and Wagener classification are suitable for the treatment, and those in group II may, if the blood pressure falls, have some measure of protection from premature cardiovascular senescence.

The drug is contraindicated in groups III and IV, and in malignant hypertension because renal failure may cause drug accumulation. It should not be given to patients over 60 years old because hypertension at this age is essentially benign and any therapy is meddlesome, or to patients with drug intolerance or cardiac and cerebral vascular complications. It is also contraindicated where adequate control of the serum level is impossible.

John Anderson

Ventricular Septal Defect with Aortic Incompetence. (Differential Diagnosis from Patent Ductus Arteriosus.) P. SOULIE, D. ROUTIER, and P. BERNAL. *Arch. Mal Cœur*, **42**, 765–780, Aug., 1949.

Ventricular septal defect may be complicated by aortic regurgitation when the aortic valve becomes implicated in the fibrosis around the septal defect. Two such cases are described. Both were incorrectly diagnosed as cases of patent ductus arteriosus and in both the patient was needlessly submitted to operation. They are reported to call attention to this possible cause of diagnostic error. The diagnostic features leading to the error were: (1) a to and fro murmur over the second and third ribs to the left of the sternum; (2) an increased pulse pressure; (3) electrocardiographic evidence of left and right ventricular hypertrophy; (4) the appearance of the heart and great vessels on radioscopy and in angiocardiograms; (5) the greater oxygen content of blood from the pulmonary artery than of blood from the right ventricle.

The difficult differential diagnosis between this condition and patent ductus arteriosus is fully discussed. The most important distinguishing point is that the double murmur does not sound like the continuous murmur with systolic accentuation which is typical of patent ductus arteriosus.

H. E. Holling

Anomalous Arterioventricular Excitation Produced by Catheterization of the Normal Human Heart. C. E. KOSSMANN, A. R. BERGER, S. A. BRILLER, B. RADER, and J. BRUMLIK. *Circulation*, **1**, 902–909, April, 1950.

Electrocardiographic abnormalities resembling those of the Wolff–Parkinson–White syndrome were produced as an intracardiac electrode was slowly withdrawn through the right ventricle during a continuous electrocardiographic recording. This anomalous auriculo-ventricular excitation might, it is suggested, be caused by contact of the catheter with the endocardial surface of the right ventricle, resulting in increased irritability of a ventricular centre (most probably in the septum) which then discharged prematurely following the slight rise in intraventricular pressure due to auricular contraction. A similar physiological mechanism might be the basis of the naturally-occurring Wolff – Parkinson – White electrocardiographic phenomenon. *A. I. Suchett-Kaye*

Electrocardiographic Observations During Cardiac Catheterization. I. R. GOLDMAN, S. G. BLOUNT, A. L. FRIEDLICH, and R. J. BING. *Bull. Johns Hopk. Hosp.*, 86, 141–168, March, 1950.

Continuous electrocardiographic records (standard limb leads) were made on 50 patients during cardiac catheterization. Only one patient did not develop any change in rhythm. Thirty patients developed auricular premature systoles, usually when the catheter tip appeared to be in contact with the auricular septum, and particularly when the catheter was passing through an auricular septal defect. Thirty-nine patients developed nodal premature systoles. Auricular tachycardia occurred in 28 patients, all of whom had congenital heart disease; it was always of short duration and did not interfere with the progress of catheterization. Nodal tachycardia occurred in 36 patients, all of whom had congenital heart disease; it also was of short duration and occurred with the catheter in the right auricle or right ventricle. Auricular flutter developed in 3 patients, but auricular fibrillation was not recorded. Ventricular premature systoles occurred in 44 patients and were often the first indication that the catheter tip had entered the right ventricular cavity. Stiffness of the catheter was found to be a factor increasing the frequency of ventricular premature systoles. Ventricular tachycardia, defined as "an uninterrupted series of three or more ventricular premature systoles," was observed in 39 patients. Except for one case in which it occurred as the catheter tip passed through the superior vena cava and right auricle, it was only seen when the catheter tip was in the right ventricle. It usually ceased with a change in the position of the catheter tip, but in 3 cases it progressed to ventricular flutter, and in one case to ventricular fibrillation before the catheter could be withdrawn. In all the cases of ventricular flutter the patient recovered, but the ventricular fibrillation (in a 10-year-old boy with rhabdomyoma of the myocardium) proved fatal. Various degrees of A-V block occurred in 16 patients, and transient right bundle-branch block in 24.

[The high incidence of arrhythmia and the almost universal response to withdrawal of the catheter emphasize the advantages of continuous electrocardiographic records during cardiac catheterization. The value of this report is enhanced by the reproduction of the recordings obtained in the terminal stages of the fatal case of ventricular fibrillation.]

William A. R. Thomson

Catheterization of the Left Side of the Heart in Man. H. A. ZIMMERMAN, R. W. SCOTT, and N. O. BECKER. *Circulation*, **1**, 357–359, March, 1950.

Catheterization of the left side of the heart presents obvious problems. The catheter must move against arterial blood pressure, and arterial spasm may be sufficiently great to prevent forward passage of the catheter. When the aortic valve has been reached the catheter must be passed through the orifice of the valve into the left ventricle in the short ejection phase (0·22 seconds) during which the aortic valve is open.

The authors chose the ulnar artery for introduction of the catheter because of its size, ready accessibility, and the fact that it could, if necessary, be ligated with impunity. Local infiltration with 1% procaine was employed. Failure to pass the catheter beyond the junction of the subclavian artery with the aortic arch occurred in one-fifth of the author's cases of aortic incompetence, but once past that point the catheter failed to pass into the ventricle in 3 cases only. In one case of aortic incompetence, catheterization caused ventricular fibrillation, which was accompanied by substernal pain, and the patient died within a quarter of an hour. At necropsy the ostium of the left coronary artery was found to be anomalous in that it was situated 3 mm. above the normal site, and it was assumed that the catheter had entered its orifice. Histological section of the heart muscle of this case revealed active rheumatic inflammation[!]. Another patient died of congestive heart failure 4 days after catheterization, but careful search at necropsy revealed no indication of trauma. *S. Oram*

Commissurotomy for Mitral Stenosis. R. P. GLOVER, T. J. E. O'NEILL, and C. P. BAILEY. *Circulation*, **1**, 329–342, March, 1950.

Earlier attempts to divide or dilate the mitral orifice were not happy in their results, but recent technical developments and modern investigation methods make the outlook much more hopeful and, in a series of 30 cases surgically treated by the authors, although 6 deaths occurred, the results to date in the survivors would appear most gratifying.

In advanced mitral disease the vegetations develop into a fibrous and thickened scar which lies along the free edge of the valve, the base remaining flexible. The surgical treatment advocated by the authors is to divide the "commissures" of the valve with a special knife attached to the right index finger, which is introduced through the left auricular appendix, blood loss being controlled by a purse-string suture tightened round the finger. Direct palpation and digital dilatation of the valve area are also possible by this method, which has certain advantages

over other methods of approach. There are obvious dangers and complications likely to arise in an intracardiac operation on an already damaged heart, and numerous technical details have to be studied in order to avoid trouble. *T. Holmes Sellors*

Heart Disease Complicated by Pregnancy. D. C. HAIG and A. R. GILCHRIST. *Edinb. med. J.*, **56**, 55–74, Aug., 1949.

An analysis is presented of material obtained for the 20-year period 1928–47, and from the follow-up examination of all patients attending the clinic during the 10-year period 1937–46. Cardiac disease was diagnosed in 1,100 cases out of a total of 80,422 pregnancies, an incidence of 1·3%. Rheumatic heart disease was found in 94%, various congenital flaws in 3·6%, hypertensive heart disease in 1·8%, and miscellaneous cardiac abnormalities in the remaining 0·6%. The mortality among patients with heart disease fell from 6·3% in 1928 to 0·9% in 1947, and it is significant that, although the over-all maternal mortality during this period had fallen from 1·1% to 0·2%, deaths from heart disease had not been reduced to the same extent, indicating that cardiac disease is now a more prominent cause of maternal mortality than formerly. There was a three-fold improvement in mortality among those patients who received adequate cardiological supervision during pregnancy, compared with those who received little attention or came under supervision only late in pregnancy.

The diagnosis of heart disease is not always easy. On follow-up examination it was found that 10% of patients who had been suspect during pregnancy had no organic heart disease. Generally the prognosis is better in the younger group of patients; over the age of 30 serious incapacity is more probable. It is for this reason that women with cardiac disease are recommended to have their babies in the early twenties.

The main purpose of antenatal supervision is to facilitate the adoption of measures to prevent the development of congestive heart failure, firstly by providing the cardiologist and obstetrician with the opportunity to see and grade all cases within the first 4 months of pregnancy, secondly by the full use of in-patient treatment in hospital and, lastly, by continued attention to the general health of the patient. The most difficult cases are those who are found to be in grade III about mid-term. Strict measures and absolute confinement to bed must be enforced for the remainder of the pregnancy in the hope that natural vaginal delivery may be safely accomplished. The method of delivery is discussed. Cæsarean section is considered to be undesirable in cardiac cases where there is no obstetrical reason for interference. Statistics are presented which indicate that the maternal mortality following Cæsarean section is double that after vaginal delivery. On the basis of the follow-up examination it appears that pregnancy may induce congestive heart failure in a woman roughly 5 to 7 years before it is due to appear in the normal course of events. The fate of patients surviving pregnancy is studied and all the evidence indicates that pregnancy does not alter the course of rheumatic heart disease. A patient with heart disease, having overcome the dangers of pregnancy, may survive for many years and ultimately die no younger than had she never borne a child. *T. N. MacGregor*

Acute Non-specific Benign Pericarditis. E. EVANS. *J. Amer. med. Ass.*, **143**, 954–957, July 15, 1950.

The author records 11 cases of acute non-specific pericarditis of obscure ætiology. Pain was the outstanding symptom in all cases and sometimes simulated that of coronary thrombosis. The pain may be differentiated because, although it may radiate widely, even to the arms, it is aggravated by movement, respiration, and sometimes by swallowing. Fever, of variable degree, was present in all the cases. Five patients had a history of recent respiratory infection. Radiologically, 4 showed cardiac enlargement (? pericardial effusion). Electrocardiographic changes were those characteristic of pericarditis. Five of the patients had more than one attack.

The author expresses the view that this condition has no relation to constrictive pericarditis, but points out that time alone will show whether this opinion is correct. He reviews some of the papers on constrictive pericarditis and points out that its ætiology is usually obscure. In an addendum, 4 further cases are described.
M. H. Pappworth

Arteriosclerotic Aortic Insufficiency. N. M. FENICHEL. *Amer. Heart J.*, **40**, 117–124, July, 1950.

Aortic insufficiency was noted in 17 patients, whose ages ranged from 59 to 75 and who had been known to have hypertension for from 4 to 25 years. In the only case examined post mortem (in a man aged 71) the aortic valves were fibrosed and calcified and the aorta was markedly sclerotic. In 13 of the cases the aortic insufficiency developed while the patient was under observation, but its advent appeared to have little influence on the prognosis. *C. Bruce Perry*

Clinical Features and Pathogenesis of Spontaneous Rupture of the Aorta. N. L. VIL'K. *Terap. Arkh.*, **22**, No. 2, 14–24, March–April, 1950.

The author discusses the clinical features and pathogenesis in 18 cases of spontaneous rupture of the aorta. Six case histories are given. The term spontaneous rupture is used for cases in which there is no trauma or neoplasm. In none of the cases was the condition diagnosed during life. There were 15 men and 3 women; most were over 40 years of age; 4 were under 40 and one patient was 15 years old. In 11 cases hypertension was present. In 11 cases the aorta ruptured in its ascending part, and in 5 cases there were multiple ruptures. In most cases the rupture led to the formation of a dissecting aneurysm. A severe migrating pain was the presenting symptom in 15 cases; other symptoms and signs included vomiting, dizziness, shock, and neurological signs (a rapidly developing paralysis of the lower limbs due to ischæmia).

A diastolic murmur was often heard in the aortic area, indicating an enlarging aorta and incompetence of the valves. Tachycardia and pulsus paradoxus developed

in some cases. The electrocardiogram did not show anything abnormal. The radiological picture was that of a progressively enlarging aorta with a double contour. The immediate cause of death was heart tamponade in 7 cases. Seven patients lived for about 24 hours after the beginning of symptoms, the others lived longer (up to 35 days in one case in which laparotomy was twice performed because the diagnosis of a perforated ulcer was made). The differential diagnosis is from myocardial infarction and ulcer perforation. In the pathogenesis, hypertension and atherosclerosis are of importanace. Congenital lesions, such as a stenosis of the aortic isthmus, may predispose to spontaneous rupture.

N. Chatelain

The Myocardium in Subacute Bacterial Endocarditis. O. SAPHIR, L. N. KATZ, and I. GORE. *Circulation*, **1**, 1155–1167, May, 1950.

The records of 76 cases of fatal subacute bacterial endocarditis from the files of the U.S. Armed Forces Institute of Pathology were studied, the purpose of the investigation being to attempt to correlate pathological changes found at necropsy with electrocardiographic changes found in life, with particular reference to the incidence of myocarditis. In all cases histological examination of the heart showed myocarditis, perivascular infiltration and fibrosis, Aschoff bodies, infarcts, and intravascular thrombi to be present in various combinations. Electrocardiographic changes that could be attributed to the myocardial damage shown at necropsy are described. It is urged that clinical evidence of myocardial change should be sought for more carefully in all cases of subacute bacterial endocarditis. *H. E. Holling*

Treatment of Congestive Heart Failure in Ambulatory Patients with Salyrgan-Theophylline Administered Orally. J. ABRAMSON, E. BRESNICK, and P. L. SAPIENZA. *New Engl. J. Med.*, **243**, 44–47, July 13, 1950.

A clinical trial was carried out, on 30 ambulant patients with congestive cardiac failure, of a mercurial diuretic in tablet form called "salyrgan-theophylline oral" (STO) each tablet containing 0·08 g. "salyrgan" (mersalyl) and 0·04 g. theophylline. All the patients had been receiving mercurial injections before treatment with STO, and all received digitalis, ammonium chloride, and a low-salt diet without fluid restriction during the trial. It was found necessary to administer the diuretic on successive rather than alternate days, treatment being started with a dose of one tablet thrice daily after meals for 3 successive days each week. Occasionally great diuresis was obtained by giving the three tablets together after breakfast. The optimum dosage was found to vary greatly from patient to patient, the largest individual dose given being 8 tablets, and the largest weekly dosage 5 tablets thrice daily for 6 days. STO completely replaced injections in 17 patients and was partly successful in 9 others. Toxicity was manifested in gingivitis and various gastrointestinal symptoms, but only one patient could not tolerate repeated trials of the drug, owing to excessive diarrhœa. *T. Semple*

Further Studies on Mechanism of Auricular Fibrillation. D. SCHERF, L. J. MORGENBESSER, E. J. NIGHTINGALE, and K. T. SCHAEFFELER. *Proc. Soc. exp. Biol. N.Y.*, **73**, 650–654, April, 1950.

This paper deals with the experimental production of auricular fibrillation and the elucidation of its mechanism. Scherf and his collaborators have already shown that auricular flutter and auricular fibrillation can be produced in dogs by the topical application of aconitine to the animal's auricle. These arrhythmias can be immediately stopped when the area of application is isolated from the rest of the auricles or cooled. These experiments (published previously) were undertaken to disprove Lewis's theory of the circus movement as the responsible mechanism of auricular fibrillation.

In the present experiments tracings were obtained from dog hearts in which auricular fibrillation was induced either by stimulation with rhythmic electrical shocks or by the application of a concentrated solution of acetylcholine to the area of the sinus node. This experimentally produced auricular fibrillation could not be stopped by cooling of the site of application of the drug. In nearly all the experiments, however, the simultaneous cooling of the sinus and A-V nodes terminated the auricular fibrillation. Furthermore, interruption of the cooling caused the auricular fibrillation to recur. It is of interest that in one instance auricular flutter appeared at the end of fibrillation and also after the cooling thermode was withdrawn before the reappearance of auricular fibrillation. The results obtained in these experiments are considered to be incompatible with a circus movement mechanism. An alternative theory of rapid stimulus formation in a centre or centres is favoured. Thus, in some forms of auricular fibrillation more than one centre of rapid stimulus formation could be active and it is also possible that rapid stimulus formation in the A-V node might be responsible for auricular fibrillation.

A. I. Suchett-Kaye

Blood Quinidine Concentrations as a Guide in the Treatment of Cardiac Arhythmias. M. SOKOLOW and A. L. EDGAR. *Circulation*, **1**, Part I, 576–592, April, 1950.

Quinidine levels were determined in blood and urine by photofluorometry in 72 patients receiving this drug. Thirty of the patients had auricular flutter or fibrillation and the remainder were given the drug for the prevention of paroxysmal arrhythmias, for example, after myocardial infarction. Normal rhythm was restored 28 times in 24 patients with auricular flutter or fibrillation. In 75% of these instances conversion took place with levels of quinidine between 4 and 9 mg. per litre of blood. To produce this effect it was usually necessary to give 0·4 to 0·6 g. of quinidine every 2 hours for 5 doses. In 5 cases conversion occurred with levels below 4 mg. per litre. Levels of 7 mg. per litre were obtained in all the cases of failure, and in 4 of these a blood concentration of 10 mg. per litre was exceeded. After a given dose of quinidine the maximum level in the blood is reached in about 2 hours and significant levels may persist for 12 to 24 hours. When the drug is given every 2 hours the rise in level in the blood after successive doses becomes pro-

gressively less, and if administration is continued the level reaches a plateau for about a week and then falls. To prevent paroxysmal ventricular tachycardia it appeared necessary to maintain a level of 4 mg. per litre of blood. *C. Bruce Perry*

Experiences with Cardiac Arrest. F. H. LAHEY and E. R. RUZICKA. *Surg. Gynec. Obstet.*, **90**, 108–118, Jan., 1950.

Cardiac arrest in the operating theatre of the Lahey Clinic has occurred 13 times in the past 7 years. Cardiac arrest may occur in any type of operation and with any anæsthetic agent or combination of agents. In this series the condition occurred during the following operative procedures: 3 chest operations; 4 abdominal operations; 6 other operations. The time during which treatment must be applied if it is to be effective is given as 3½ minutes, and any delay beyond this results in permanent changes in psychic behaviour. Interruption of the cardiac action for over 8 minutes is incompatible with life for more than a few hours.

The plan of action suggested is as follows: (1) artificial respiration, with 100% oxygen; (2) immediate cardiac massage by the surgeon; (3) injection of procaine and adrenaline (epinephrine); (4) general treatment, including intravenous administration of fluids and adoption of a 5 to 10 degree Trendelenburg position. Procaine and adrenaline, if immediately available, are injected by cardiac puncture, but no time should be wasted in waiting for sterile syringes and solutions. The airway must of course be unobstructed, and an endotracheal tube inserted if not already in use.

In all of the 13 cases reported cardiac action was restored, but in only 5 cases has there been recovery with normal mentality. The most common complication of cardiac massage is ventricular fibrillation. This may be treated by injection of 5 ml. of 2% procaine into the cavity of the right heart and continuation of the massage. *F. d'Abreu*

Tussive Syncope. Observations on the Disease Formerly Called Laryngeal Epilepsy, with Report of Two Cases. W. S. MCCANN, R. A. BRUCE, F. W. LOVEJOY, P. N. G. YU, R. PEARSON, E. B. EMERSON, G. ENGEL, and J. J. KELLY. *Arch. intern. Med.*, **84**, 845–856, Dec., 1949.

Tussive syncope is a term now suggested as preferable to Charcot's "laryngeal vertigo." Paroxysms of coughing or even forced expiration against an impediment may cause congestion of the cerebral veins, decrease in cardiac output, abnormally high pressure in the right ventricle, and anoxæmia. Such a course of events may bring about syncope and convulsions. In addition, there may be, during bouts of coughing, spasm of the pulmonary artery, which will naturally worsen the clinical manifestations. This spasm may be associated with nicotine poisoning in certain cases.

The supporting evidence for these contentions is to be found in a full account of 2 patients, one of whom showed this full clinical syndrome of tussive syncope and the other acute elevation of pressure in the right ventricle to 270 mm. Hg during attacks of coughing, with a history of syncopal attacks occurring after severe bouts of coughing, usually following meals. *G. F. Walker*

The Cough Syndrome. Faintness and Loss of Consciousness from Coughing: the so-called Syndrome of Laryngeal Vertigo. CHARLES BAKER. *Guy's Hosp. Rep.*, **98**, 132–167.

Nine patients who suffered attacks of loss of consciousness and faintness from coughing are reported. They were collected without difficulty within two years, so the condition is not rare.

One hundred and sixty-eight reported cases are here analysed, with the 9 new cases. The whole group comprises a clear-cut clinical picture.

It occurs predominantly in men, and in the second half of life, especially in plethoric, obese, emphysematous men with a chronic cough. Good living, hard living, excessive smoking and drinking are commonly found. Cough is the provoking factor.

The prognosis is good and wider recognition of this syndrome will prevent invalidism and unnecessary restriction which might result from a mis-diagnosis of epilepsy or cardiovascular disease.

It is suggested that the attacks are due to prolonged increased intrathoracic pressure due to violent coughing against a closed glottis; there is a diminished venous return to the right heart which is mirrored in the venous engorgement in the neck.

As this syndrome is neither laryngeal in origin nor vertiginous in its effect, the term *Laryngeal Vertigo* used by Charcot in his description in 1876 should be abandoned. A simple title is needed which may help this not uncommon syndrome to be better known. To include both faintness from coughing and unconsciousness from coughing, the non-committal title of The Cough Syndrome is suggested. *Maurice Campbell*

Hypothyroidism Produced by Radioactive Iodine (I^{131}) in the Treatment of Euthyroid Patients with Angina Pectoris and Congestive Heart Failure. H. L. BLUMGART, A. S. FREEDBERG, and G. S. KURLAND. *Circulation*, **1**, 1105–1141, May, 1950.

The therapeutic results are reported on the induction of hypothyroidism by the administration of radioactive iodine (I^{131}) in 18 patients with intractable angina pectoris or advanced congestive heart failure. After the production of hypothyroidism the patients were observed for periods ranging between 7 and 24 months.

The patients were given carrier-free I^{131} orally in single or divided doses to a total of 25·5 to 150 mc., the average dose being 54·4 mc., of which the average retention was 17·9 mc. Mild thyroiditis sometimes followed its administration but otherwise there were no toxic effects. The therapeutic effects appeared 5 weeks to 5 months later and the hypothyroidism produced was persistent. In general the patients were ambulatory during treatment, only those who were seriously incapacitated and had not been helped by standard measures being treated. The symptoms were strikingly lessened or abolished in 8 of the 13 patients with intractable cardiac pain; in the

other 5 the angina was relieved when the patient became myxœdematous, but recurred when thyroid was given to relieve the discomfort of the myxœdema. Of the 5 patients with congestive heart failure only 3 were improved. *H. E. Holling*

Myocardial Infarction. Observations on One Hundred Patients who Survived up to Six Years. G. Y. MILLS, A. J. SIMON, F. CISNEROS, and L. N. KATZ. *Arch. intern. Med.*, **84**, 632–639, Oct., 1949.

This is a follow-up study of 100 patients in the Michael Reese Hospital, Chicago, who survived for from 1 to 6 years after acute myocardial infarction. The majority were working at their former jobs.

The electrocardiograms showed little restitution towards normal in 77, partial restitution in 14, and complete change to normality in 9. The incidences of hypertension and of angina pectoris were similar in the three groups and bore no relation to the behaviour of the cardiogram, but heart failure was practically confined to those whose cardiograms showed little restitution. A conspicuous Q wave was present both in the cases showing persistent gross changes and in the cases of partial restitution, but there was no abnormal Q wave when restitution was complete. *Paul Wood*

Direct Electrocardiograms from the Human Heart in Situ. Comparison of Direct Leads with Precordial Leads. G. E. HEIN and J. C. REAVIS. *Circulation*, **1**, 964–969, April, 1950.

Direct electrocardiographic records from the surfaces of the human heart were compared with tracings from precordial leads in corresponding positions taken before the heart had been exposed. A close relationship between the direct and the precordial tracings was demonstrated in a case of constrictive tuberculous pericarditis. The direct records were taken after pericardectomy and partial stripping of the epicardium had been carried out.

A. I. Suchett-Kaye

The Use of Anticoagulants in Acute Coronary Insufficiency or Impending Myocardial Infarction. E. S. NICHOL. *Sth. med. J.*, **43**, 565–574, July, 1950.

The author believes that impending myocardial infarction may be recognized clinically by acute exacerbations, or acute development, of the syndrome of angina pectoris. Over a 3-year period 41 patients presumed to be showing the premonitory signs of infarction have been treated by the author with anticoagulants. The previous history and subsequent course of the condition made it highly probable that the diagnosis was correct. Some showed inversion or flattening of T waves in the electrocardiogram taken in the acute phase, normal appearances returning as the attack passed off, and S–T depression was also common. After initial administration of heparin, clotting was controlled by dicoumarol in most cases, though in some heparin was given throughout, the period of treatment ranging from 2 to 82 weeks. A fair degree of relief of anginal pain was obtained in all but 3 patients; 2 of the 41 patients developed transmural myocardial infarction after anticoagulant therapy had been started; 24 developed clinical manifestations of some endocardial necrosis; and 4 died with acute myocardial infarction 7 days to 10 months after stopping anticoagulant treatment.

The author admits the difficulty of differentiating with certainty between attacks of so-called " coronary failure " and frank myocardial infarction. He emphasizes the frequent benefit that seems to follow anticoagulant therapy. *J. McMichael*

The Electrocardiogram in Old Age. P. HAGEN and Z. FREEMAN. *Med. J. Aust.*, **1**, 499–503, April 15, 1950.

With unipolar leads, an electrocardiographic study was made of 56 " clinically healthy " old men, aged 65 to 93 years (average 68 years). All were ambulant. The systolic blood pressure ranged from 190 to 100 mm. Hg, and the diastolic from 90 to 50 mm. Hg. The following abnormalities were detected: in 4 cases, right bundle-branch block; in one case, right ventricular hypertrophy; in 2 cases, first-degree heart block; in 2 cases, S–T depression in the præcordial leads; in 6 cases, flat or inverted T waves in the præcordial leads. Attention is drawn to the fact that, according to this investigation, " T wave changes are not a necessary accompaniment of aging, and most healthy old men have perfect electrocardiographic records." *William A. R. Thompson*

Electrocardiograms of Normal Children. With Special Reference to the aV Leads and Chest Leads. J. L. SWITZER and M. BESOAIN. *Amer. J. Dis. Child.*, **79**, 449–466, March, 1950.

Electrocardiograms were obtained from 52 normal children in an institution; they were of both sexes and under 15 years in age. In addition to the standard limb leads, the aV limb leads and 9 precordial leads were used. Tables are given summarizing the rhythm and rate of the heart, and the contour, height, and duration of the deflection in each of the 15 leads. These data are to be used as a base-line for studying abnormalities in children.

The findings agree with those of previous workers. The most interesting findings in the ventricular complex were in the T waves in the precordial leads which could be negative, diphasic, notched, or bifid. A Q wave frequently appeared, particularly in the youngest children.

H. M. Sinclair

Electrocardiographic Patterns in Hypopotassemia: Observations on 79 Patients. S. BELLET, W. A. STEIGER, C. S. NADLER, and P. C. GAZES. *Amer. J. med. Sci.*, **219**, 542–558, May, 1950.

Serial electrocardiograms were recorded in 79 cases of hypopotassæmia, in 69 of which the condition was due either to diabetic acidosis (35 cases) or to vomiting secondary to intestinal obstruction (34 cases). Five electrocardiographic patterns pathognomonic of hypopotassæmia are described: (1) depression of the ST segment; (2) inversion of the T wave; (3) normal amplitude of T wave with prolongation of Q–T interval; (4) low ampli-

tude of T; (5) persistence of U wave. Patterns 1 and 2 were the most common, occurring in 80% of cases. Pattern 1 was found most commonly in vomiting, pattern 2 in diabetic acidosis. The U wave is considered to furnish important evidence of hypopotassæmia, having been present in 31 cases. The cardiographic changes of hypopotassæmia were immediately reversible by administration of potassium.

William A. R. Thompson

Pulmonary Hypertension in Chronic Pulmonary Emphysema. C. W. BORDEN, R. H. WILSON, R. V. EBERT, and H. S. WELLS. *Amer. J. Med.*, **8**, 701–709, June, 1950.

Direct measurement of the pulmonary arterial pressure was carried out by means of catheterization in 24 men with chronic pulmonary emphysema, who were moderately or completely disabled by effort dyspnœa. The average age of the group was 55, the range being 33 to 70 years. Pressure was measured by means of a Hamilton manometer and optically recorded. The degree of emphysema was estimated by measuring the total lung volume, vital capacity, and functional residual air.

The mean pulmonary diastolic pressure was 22 ± 7 mm. Hg, and the range 15 to 37 mm. This was distinctly higher than in a group of 12 control subjects, in which the values were 8·8 and 6 to 11 mm. Hg respectively. There was no demonstrable correlation between the degree of pulmonary hypertension and the severity of the emphysema, but the average pulmonary arterial pressure was higher in 8 patients who had shown signs of right heart failure than in the others. On the basis of a normal arterio-venous oxygen difference and a normal oxygen consumption the authors concluded that the cardiac output was not raised in these cases. Again, they were unable to find any correlation between the degree of oxygen unsaturation and the arterio-venous oxygen difference.

Paul Wood

Observations on the Management of Hypertension by the Kempner Rice Diet. C. R. WILLIAMSON. *New Engl. J. Med.*, **243**, 177–182, Aug. 3, 1950.

This article described in detail some interesting observations on 67 patients receiving the Kempner rice diet for hypertension. Only those subjects were chosen in whom the diastolic pressure was above 100 mm. Hg in repeated determinations. After a preliminary period of observation of 3 weeks without diet, and despite the fact that they were not confined to bed, 37 of the 67 were eliminated from the study as their diastolic pressure had fallen below 100 mm. Hg. The diet contained 200 g. (dry weight) of rice, with fruit, sugar, and fruit juices in sufficient quantities to provide 2,500 calories and 1,000 ml. of fluid. Iron and vitamin supplements were also given.

After 19 more patients had been eliminated either owing to complications such as heart failure or because they could not stick to the diet, the remaining 11 were observed over 6 or more weeks. In all of these cases there was loss of weight and symptomatic improvement, but in 7 of the 11 cases no fall in diastolic pressure was observed. In the 4 cases in which a fall in diastolic pressure did occur, the addition of salt-free protein to the diet produced no change in blood pressure. Capsules were given to these 4 patients which on some occasions contained lactose, on other salt. In 3 cases the addition of 8 to 10 g. of salt to the diet daily produced a rise in the diastolic pressure, in 2 a rise in the systolic pressure, and in one no change in either. Withdrawal of the salt caused a return to the previous low level. Case histories are given. The author points out the importance of the psychological and malnutritional aspects of the diet in contributing to its success.

G. S. Crockett

Thiocyanate in Hypertension. Blood Pressure Behavior After Withdrawal of the Drug, and Serial Electrocardiograms as Criteria of Response. E. J. FISCHMANN and A. FISCHMAN. *Amer. Heart J.*, **39**, 477–483, April, 1950.

A prolonged follow-up study of 50 thiocyanate-treated hypertensive patients, with a control group of 36 untreated patients, revealed that withdrawal of the drug is not always followed by a rise in blood pressure or a return of symptoms. This suggests that to attribute the improvement to thiocyanate may not be entirely justified; the falls in blood pressure may equally be related to the effects of rest and familiarity with blood pressure measurements. In only 11 cases of the present series could a causal connexion be found between thiocyanate therapy and symptomatic improvement. In none of the treated cases was there the reversal of electrocardiographic changes which is known to occur in hypertensive patients after sympathectomy. Moreover, in the control series not treated by this drug a spontaneous fall in blood pressure took place in one-third of patients observed over several months. The authors are unable to confirm the previously accepted suggestion that thiocyanate is a natural depressor.

J. L. Lovibond

Prognosis of Vascular Hypertension. A Nine Year Follow-up Study of Four Hundred and Eighteen Cases. R. FRANT and J. GROEN. *Arch. intern. Med.*, **85**, 727–750, May, 1950.

Results are given of a follow-up examination of 418 patients with hypertension who were re-examined after a period of 8 to 9 years. The death rate for men with essential hypertension exceeded the normally expected death rate in the same age groups by 102%; for the women this figure was 91%. Chronic nephritis increased the death rate in men by 587% and in women by 150% in excess of the normal. Hypertension related to toxæmia of pregnancy carried a mortality of 155% in excess of the expected. The total excess mortality for patients with hypertension of all types was 233% for the men and 201% for the women.

Analysis of the cases of essential hypertension showed that the mortality increased with increase of both systolic and diastolic blood pressure. A similar, even more constant, parallelism was found in the ophthalmoscopic picture. The findings of Keith, Wagener, and Barker for the prognostic significance of the retinal changes

could be confirmed. The condition of the fundus of the eye is a better guide for the prognosis of hypertension than the increase in blood pressure. Complications such as heart disease, albuminuria, diabetes and obesity had a definite influence on the prognosis. Hypertension accompanied with obesity appeared to be prognostically more favourable than the same hypertension in patients whose weight was normal or low. Hypertension in young subjects carries a relatively shorter life expectancy than high blood pressure in old age.

The progress of the disease in the patients who were still alive at the time of the re-examination will form the subject of a separate paper.—(Authors' summary.)

Action of a Mercurial Diuretic on the Blood Pressure in the Right Heart in Cardiac Disease. L. SCÉBAT, P. MAURICE, and J. LENÈGRE. *Arch. Mal. Coeur*, **42**, 1149–1153, Dec., 1949.

Action of Morphine on the Blood Pressure in the Right Heart in Cardiac Disease. L. SCÉBAT and J. LENÈGRE. *Arch. Mal. Coeur*, **42**, 1154–1156, Dec., 1949.

Brief accounts are given of the effects of a mercurial diuretic (" novurit ") and of morphine on right heart pressures in cases of various types of heart disease with different degrees of cardiac failure. Right auricular or ventricular pressures were measured by cardiac catheterization and the drugs were injected slowly through the catheter.

The injection of the mercurial diuretic was followed by a fall in right auricular and ventricular pressure, variable in time of onset, in degree, and in duration. The authors remark that of all the drugs investigated (including digitaline, theophylline, and morphine) the mercurial diuretic provoked the greatest and most lasting falls in right heart pressure. The injection of morphine usually provoked a smaller and more transient fall, but in some cases caused a rise in both auricular and ventricular pressures. *R. T. Grant*

A Systolic Murmur Heard over the Lower Abdominal Aorta: its Significance in Peripheral Vascular Diseases. R. J. POPKIN. *Angiology*, **1**, 244–246, June, 1950.

The author points out that a systolic bruit over the abdominal aorta has often been noted by previous authors, but finds few, if any, references to its clinical significance.

The bruit is best heard with the patient lying on his back, and the best site to listen is a few centimetres below and to the left of the umbilicus. The systolic bruit is variable in degree and duration, is not affected by posture, and is rarely accompanied by a thrill.

Out of a consecutive series of 35 patients with subjective and objective signs of peripheral vascular disease (20 had arteriosclerosis), a bruit was heard in 22 cases. In a control series of 35 patients without organic peripheral vascular disease, no murmur was heard over the abdominal aorta. The author maintains that, aneurysms and coarctation of the aorta excluded, such a bruit is pathagnomonic of organic peripheral vascular disease. The abdominal aorta is the most frequent site of atherosclerosis and this change is found in some degree in the majority of people above 40. Radiological evidence of calcifications of the abdominal aorta was present in " practically all cases " of arteriosclerosis in which the bruit was heard (no figures are given). The author discusses the possible mechanical factors responsible for the bruit. *M. H. Pappworth*

Truncus Aorticus. Clinical and Radiological Diagnosis. P. SOULIÉ, J. NOUAILLE, O. SCHWEISGUTH, and M. TOUCHE. *Bull. Soc. méd. Hôp. Paris*, **66**, 919–944, June 2, 1950.

The differentiation of the condition of " truncus aorticus " (atresia of the pulmonary artery with pulmonary blood supply through the bronchial arteries) from Fallot's tetralogy has become a matter of practical importance if unnecessary surgical exploration is to be prevented. The authors report 6 cases and stress the following diagnostic points: constant subclavicular murmur (not present in all cases); extreme aortic configuration of the heart shadow on radioscopy, with prominent aortic knuckle; absence of hilar shadows. On performing angiocardiography they found rapid filling of a large aorta, absence of the pulmonary artery, and delayed entry of the contrast medium into the pulmonary circulation.

G. Schoenewald

Peripheral Arterial Embolism. A Study of 330 Unselected Cases of Embolism of the Extremities. H. HAIMOVICI. *Angiology*, **1**, 20–45, Feb., 1950.

The author presents a critical evaluation of the results of embolectomy and various medical procedures in relation to the natural course of peripheral arterial embolism. He found that the heart was the source of the embolism in 96% of cases. An initial diagnosis of acute arterial thrombosis is often revised when the clinical course or necropsy reveals a " silent " myocardial infarction with mural thrombi. Survival of the limb after embolic occlusion depends on the site and extent of the block; embolism at arterial bifurcations is particularly dangerous. Sudden distension of an artery by an embolus sets up a chain of events that includes vasospasms, secondary thrombosis, and structural changes in the arterial wall.

In a series of 330 cases clinical onset was characterized by sudden pain in 59% of patients and by sudden appearance of paræsthesæ in 22%; onset was progressive in 12%, and in 6% the occlusion was " silent." Embolism was followed by complete recovery in 30%, by chronic post-embolic ischæmia in 17%, by gangrene in 28%, and by early death in 11%. Concurrent venous thrombosis was present in at least 7% of the cases.

Among medical measures, induction of vasodilatation either by drugs such as papaverine or by sympathetic nerve block and anticoagulant therapy is the most valuable. Should these measures fail to restore collateral circulation within 2 to 4 hours, embolectomy should be performed without further delay. Local application of heat and elevation of the limb are harmful, and results in this series suggest that refrigeration in the early stage of the disease is also contraindicated. *T. Semple*

Electrocardiography Fundamentals and Clinical Applications. LOUIS WOLFF, M.D., Visiting Physician, Consultant in Cardiology and Chief of the Electrocardiographic Laboratory, Beth Israel Hospital. Philadephia and London: W. B. Saunders Co., Ltd., 1950. Pp. 186; Figs. 110. 22*s*. 6*d*.

Experience in teaching medical students made it clear that the explanation of basic principles was a more acceptable introduction to a difficult subject than an attempt to teach a list of diverse electrocardiographic patterns. The purpose of this book, then, is a purely practical one; to teach the reader by the essence of these lectures the physiological background of electrocardiography and its applied clinical interpretation. The author begins by describing the electrical phenomena of muscle contraction applicable to the interpretation of the electrocardiogram and proceeds to the concept of unipolar leads and the methods and reasons for exploring the different parts of the body. The second portion of the book tells how these principles apply to analysis of tracings commonly observed in practice. It is a clear, simple and understandable exposition of a subject which only too easily becomes complicated or incomprehensible.

J. L. Lovibond

Physiology in Diseases of the Heart and Lungs. M. D. ALTSCHULE, Assistant Professor of Medicine, Harvard Medical School; Visiting Physician and Research Assistant, Beth Israel Hospital. Harvard University Press (London: Geoffrey Cumberlege), 1949. Pp. 368. 40*s*.

The book is based on lectures given by the author to Harvard medical students. It is designed primarily as a review of data included in scientific papers and not of the conclusions derived from them, since these can mislead. A great deal of ground is systematically covered, providing a basis for consideration of the various disorders of cardiac and pulmonary function; specific symptoms and therapeutic mechanisms are discussed and explained. By giving in this way a complete and stimulating review, very fully annotated by references, the author has provided a useful work which will be of value not only to medical students but to investigators and teachers in this field.

J. L. Lovibond